

1 study, you can imagine, we had to add new centers.

2 All these centers were experienced
3 investigators. Many of them are well known to you as
4 universities, but we wanted a blend of both
5 universities as well as routine clinical practices
6 that had expertise in lupus. So both these studies
7 have combined that.

8 Regarding your question on cigarette
9 smoking, keep in mind that the first study started in
10 1994, and I think, unfortunately, people's awareness
11 of the deleterious effects of cigarette smoking
12 probably has taken some years to take hold, and lupus
13 patients nowadays are probably much more cognizant of
14 it than they were in 1994 of the risks.

15 DR. JOHNSON: One other point: I think
16 maybe this is obvious to most people, but the average
17 steroid dose is quite different in these two trials,
18 too. There was only about three milligrams versus 13
19 or 15 or something like that in the first trial.

20 I don't know if there was a systematic
21 difference in the duration of disease from the onset
22 of diagnosis, though. Did you analyze that?

23 DR. GURWITH: Probably not.

24 ACTING CHAIRMAN HARRIS: Are there any
25 other questions? Yes, Dr. Liang.

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1 DR. LIANG: We are all sort of skirting
2 around the issue of co-therapy, and we were just
3 checking for ourselves in terms of drugs that may have
4 been started before the trial period that may have had
5 a buzz or an effect during the trial period.

6 We note that it's only six weeks preceding
7 the recruitment into the study, and you are adding
8 things that may have a delayed onset, you know, like
9 antimalarials and what-not. Do you have any sense of
10 that?

11 I just would -- You would have to inspect
12 the patient by patient data, and I'm asking a lot, but
13 I don't know if you -- The same thing is --

14 DR. PETRI: This is a randomized trial,
15 though. So if that were to happen, we have no reason
16 to suspect that it wouldn't be balanced.

17 I can tell you more about --

18 DR. LIANG: No, but that balance statistic
19 as a group, as a group number.

20 DR. PETRI: There is no way to capture
21 that, though, from what the company has. I can tell
22 you, at my own site, though, the patients who I
23 enrolled were my own long term, established lupus
24 patients, and I didn't have any patient who had just
25 started an anti-malarial who was then enrolled in this

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1 trial.

2 DR. LIANG: Then the other thing,
3 Michelle, you know, you gave us the n of one, which is
4 the way we sort of usually relate to these things
5 where you showed us the steroid dose. Steroids are
6 such a 900-pound gorilla in any lupus trial. You
7 know, 5 milligrams of prednisone makes a big
8 difference in quality of life and everything else.

9 I wondered if you have looked at the
10 individual data points on these patients to see --
11 especially as we are all concerned about the fact
12 there was no protocol for the steroid escalation
13 phase. Have you looked at the curves, you know, to be
14 comfortable that the effects were not contaminated by
15 changes of steroid or any other --

16 DR. PETRI: Well, let me address one part
17 of your question, which is the need for an algorithm
18 for prednisone increases. It's obvious now it would
19 have been nice to have an algorithm for prednisone
20 increases.

21 I have to tell you, though, knowing the
22 lupus community, I'm not sure how many investigators
23 would have bought into this study if there had been an
24 algorithm for prednisone increases. It was hard
25 enough to get us all to agree with the algorithm for

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1 prednisone reduction.

2 We all believe we know how to do it. We
3 all do it a little bit differently. So, yes, in
4 retrospect there should have been an algorithm for
5 prednisone increases, but again are we going to do it
6 by organ system, severity?

7 These are such complex clinical trial
8 design issues that I think we all understand why we
9 don't yet have an FDA guidance document.

10 DR. LIANG: No, we can't wring the towel
11 over things that have happened, but we can at least
12 look at the data to see what those trends were, what
13 they were in the individual patient, because you
14 collected that data.

15 DR. PETRI: Let me ask Dr. Gurwith to
16 further respond.

17 DR. GURWITH: I'm still not clear what
18 your question is.

19 DR. LIANG: Well, I guess it starts with
20 the fact that all of us who take care of patients know
21 that, you know, small doses of prednisone can make a
22 major impact on the quality of life and also disease
23 manifestations.

24 I like that curve where you showed us that
25 aberrant case where the non-study physician bumped the

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1 steroids to some astronomical level, but I'd like to
2 be assured that you looked at that for individual cases
3 during this trial.

4 DR. GURWITH: Dr. Hurley alluded to that
5 in his talk. There were seven patients who had 100 --
6 those are the outliers.

7 DR. LIANG: No, no. I'm not actually
8 talking about the outliers of that. I'm talking about
9 like five milligrams of prednisone.

10 DR. GURWITH: So you are asking what
11 happened to the steroids --

12 DR. LIANG: Actually, I'm looking not for
13 a statistical normative statement. I'm looking for
14 reassurance that someone who has seen patients has
15 seen those individual data points, I guess, or
16 individual case histories.

17 DR. SCHWARTZ: Dr. Liang, are you
18 questioning how many complied with the algorithm? Is
19 that it?

20 DR. LIANG: No. I'm just asking for a
21 description of the steroid dosing that occurred during
22 the trial which may have confounded our -- which might
23 confound our interpretations.

24 DR. SCHWARTZ; I'm not sure I can answer
25 that, because as you know, there was a protocol

1 specified algorithm.

2 DR. LIANG: Right. For diminishing
3 steroid dosing, but not for increasing.

4 DR. SCHWARTZ: Well, there was no
5 algorithm. We couldn't prescribe that.

6 DR. LIANG: I understand that. We've gone
7 through that five times, but I'm looking for the data.
8 I'm not looking for an editorial. But I wondered if
9 you did it.

10 ACTING CHAIRMAN HARRIS: Well, just one
11 reply, and then we'll go on. Okay, go ahead.

12 DR. GURWITH: We did look at every
13 individual patient's profile, you know, how they go
14 up. And you know, you cannot -- the random -- to some
15 sense, we do see some outliers, but they go up.
16 Remember that most of the time, it's the investigator.
17 Sometimes it's the referring physician that makes the
18 steroid dose change.

19 ACTING CHAIRMAN HARRIS: Dr. Sherrer?

20 DR. SHERRER: Just one comment on that.
21 Couldn't you approach that by looking at -- increase
22 in steroids versus those whose steroid dose was stable
23 throughout the trial?

24 DR. PETRI; Because we have two trials
25 with such differing trial designs, are you talking

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1 about 94-01 where there was the required prednisone
2 reduction if the SLEDAI was constant or improved?

3 DR. SHERRER: No. I'm trying to get at
4 Matt's question, actually, in both. Since you didn't
5 have an algorithm for steroid increases, if you look
6 at the data in a subgroup of patients who had any
7 increase in steroids versus the people who had either
8 reduction in the second study or who had no change or
9 reduction in the first study.

10 DR. PETRI; Well, remember that our
11 responder in the first study was a sustained
12 prednisone reduction for two months, including the
13 last visit. So if someone had a prednisone increase,
14 they are not even a responder. They violated the
15 definition of the response in the first study.

16 DR. STRAND: Blinded, I looked at all of
17 the steroid doses to determine responders before we
18 had done any unblinding or treatment groups. You saw
19 the examples where either a patient went to another
20 physician or they had coverage for stress doses
21 because of something that happened, but the most
22 typical thing was that they had been tapered down,
23 they flared, and then they were given a high dose of
24 steroids to bring them back down again.

25 The doses were not all that high, but

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1 relative to where they started in the study, say at
2 7.5 or ten, it was possible to go up to 20, 25, and
3 thereby have a 200 percent increase. And there were -
4 - The total dose allowed was 30 milligrams, with the
5 idea that over seven to possibly nine months there
6 would be time to taper, provided patients stayed
7 stable the entire time.

8 ACTING CHAIRMAN HARRIS: Dr. Brandt.

9 DR. BRANDT: Just to pursue the same issue
10 with regard to modest increases that might be
11 initiated by the patients themselves or by an outside
12 doctor, would those be considered protocol violations,
13 and what sense do you have of how much of that,
14 between visits, was occurring, not based on the
15 judgment of the investigators?

16 DR. STRAND; It was very complicated. So
17 that was a good question. There was actually -- the
18 actual dose and the prescribed dose, and those were
19 both looked at because of that very issue, that
20 patients would come back and they would have to answer
21 what they had been taking, and the physician would
22 then score the SLEDAI, etcetera, and prescribe a dose.
23 Then this was checked at the next time.

24 So there were some of these changes, but
25 if they were for longer than ten days, they were

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1 definitely a protocol violation, etcetera, and if
2 someone had an issue of flare, a symptom, they were
3 required to come in and have a new SLEDAI scored.
4 That meant all the lab data and everything else.

5 So as much as could be controlled was, and
6 from that point of view, asking for doses to be stable
7 for the last two months of the study was a stringent
8 kind of responder way of looking at the data.

9 DR. BRANDT: Thank you.

10 ACTING CHAIRMAN HARRIS: Are there any
11 other questions? I wanted to ask one. I may have
12 missed it, and it may be an easy question, but
13 something about the usage of prednisone in the
14 patients with SLEDAIs of zero to two. Was there any
15 imbalances, and did they look different from those
16 with steroid doses above two?

17 DR. PETRI; In the first study, of course,
18 one had to have had a prednisone dose of 10 to 30
19 milligrams to get into the study, and there was no
20 imbalance in terms of the SLEDAI scores of zero, one,
21 two, versus the population greater than two.

22 DR. ELASHOFF: One very quick question.
23 Do you have any data on complement activation on DHEA?

24 DR. SCHWARTZ: We do. Yes, can we pull
25 the slide up? I don't know.

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1 Recently, on the same study that you saw
2 in the normal volunteer women who were treated for 28
3 days with DHEA, we did actually send all 14 of those
4 women out to Denver National Jewish Hospital. We got
5 those results back. We're trying to pull up the
6 slide.

7 In essence -- and they were reviewed by
8 Dr. John Atkinson at Washington University as well.
9 We did not see an increase in complement activation
10 products in these patients. In fact, two or three of
11 them had profound reductions, and that was also
12 suggestive of what Dr. Atkinson and we felt, was that
13 this is consistent with an effect on hepatic
14 synthesis.

15 Again, these are non-lupus patients.

16 DR. ELASHOFF: Right. You don't have it
17 in your lupus patients?

18 DR. SCHWARTZ: No, we don't. We do,
19 actually. Dr. Petri -- yes, we do. We sent out also
20 on Michelle's patients the same assay on maybe four or
21 five of them, and we did not see an increase in
22 complement activation products in them either. Yes,
23 some of them did; some didn't. We have sort of
24 controls, but we did not see this increase either.

25 Michelle, do you want to say anything

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1 further about that?

2 DR PETRI: This is the advantage to having
3 the Hopkins lupus cohort, because we had stored serum
4 and plasma on all of our patients, and that was the
5 source of the samples that were sent for these
6 complement split product assays.

7 DR. SCHWARTZ: And how was the plasma
8 collected then, because this is off stored rather than
9 prospectively? Everybody realizes how crucial that is
10 to complement measurements. I don't doubt the second
11 study prospective --

12 DR. PETRI: Because we are doing lupus
13 anticoagulant assays on the plasma, the blood is
14 double-spun within four hours of collection and stored
15 at -70 degrees.

16 DR. SCHWARTZ: Is it stored in the cold?

17 DR. PETRI: Yes, sir.

18 DR. SCHWARTZ: Same for the normal
19 volunteer study.

20 DR. LIANG: These activity measures, you
21 know -- you can get the same number. Some things get
22 better, and some things get worse, and it may change.
23 Did you notice that in the trial, because I'm sure you
24 had the raw data. But did you see that kind of trend?

25 DR. GURWITH: In other words, say we are

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1 looking at the organ level metric, because it's said
2 to happen.

3 DR. PETRI: -- the descriptors in the
4 SLEDAI or SLAM change.

5 DR. GURWITH: In the patients who were
6 zero, one and two, did their descriptors change?

7 DR. LIANG: Well, actually, any of the
8 patients.

9 DR. GURWITH: Sure, they changed.

10 DR. LIANG: They changed. I'm starting
11 with that point. But did some things get better, and
12 other things get worse, and did that change over --

13 DR. GURWITH: Yes. Yes, definitely. I
14 mean, the --

15 DR. LIANG: And so how did you deal with
16 that?

17 DR. GURWITH: Well, that's why we use a
18 composite. I mean, we have the SLEDAI or the SLAM.
19 As you know, it is a composite, and the composite
20 score analyzes all of it. What you are asking is how
21 -- if a patient's rash got worse and her arthralgia
22 got better, how we evaluated her? Is that --

23 DR. LIANG: Well, that's one, but I think
24 you had the data to display it as well. I mean, I
25 think this is an issue of analysis as well the display

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1 of the --

2 ACTING CHAIRMAN HARRIS: Dr. Liang, I
3 think there is a slight --

4 DR. LIANG: Oh, I'm sorry.

5 DR. GURWITH: That really doesn't address
6 it. We tried doing that, especially in 94-01,
7 looking at the individual descriptors, do we see a
8 mean change in one group of descriptors, and we really
9 couldn't see a pattern.

10 DR. JOHNSON: Are you asking were there
11 certain organ dominant subgroups of lupus patients who
12 responded better or worse? Is that what you're
13 asking?

14 DR. LIANG: Well, that's another area.

15 DR. PETRI: I think that this is one case
16 where that adverse event slide I showed you might be
17 instructive, because you remember that many things
18 were less common as adverse events in the GL701 group,
19 including rash, joint disorder, nasal ulcers,
20 myalgias. But I don't think there is any analysis of
21 the fact that a patient might have changed which organ
22 systems were active during the year of the 95-02
23 trial.

24 DR. LIANG: But you had the data, I think,
25 to do that.

1 DR. PETRI: Subgroup analyses could be
2 done, but I think the important thing is SLEDAI and
3 SLAM are composite indices. If the scores go down,
4 overall I think there is an intuitive feeling that
5 that patient is better.

6 DR. BRANDT: Between the two studies, what
7 proportion of patients were anti-phospholipid antibody
8 positive, and did that make any difference to the
9 results whatsoever?

10 DR. GURWITH: About two-thirds were
11 positive, and we haven't analyzed in terms of outcome
12 for those that were positive or negative. We have
13 looked at changes in phospholipids, and in general
14 they went -- They went down a little more in the GL701
15 patients, as you see on this slide, but that's a
16 change from normal to high; and we didn't see any
17 clinical events to suggest anti-phospholipid syndrome.

18 ACTING CHAIRMAN HARRIS: And there was a
19 single patient --

20 DR. PETRI: May I add one thing to this?
21 You can see that the GL701 patients were less likely
22 to change from normal to high for IgG, the most
23 important isotype.

24 ACTING CHAIRMAN HARRIS: Okay. Now while
25 we are thinking, let's seize this moment. We are

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1 going to have a lot of time for discussion this
2 afternoon.

3 The FDA -- you can begin your
4 presentation.

5 DR. WILSON: What I am going to be
6 discussing over the next few minutes is the
7 nonclinical studies that were submitted in support of
8 the NDA for GL701 or prasterone.

9 DHEA has a lot of -- has clear tropic
10 activity. I am going to be focusing on the toxicology
11 studies, and I am not going to be addressing some of
12 the other pharmacological activity or the efficacy
13 studies.

14 I would like to begin my talk by providing
15 a framework with respect to the recommendations that
16 we generally have for the -- of the studies to support
17 an NDA for a new molecular entity that is given on a
18 chronic basis. Then I am going to focus specifically
19 on the nonclinical package for GL701 and conclude the
20 last few minutes with a discussion on DHEA and its
21 potential relationship to carcinogenicity.

22 The general recommendations that we make
23 for nonclinical studies are outlined in the
24 International Conference on Harmonization Guidance M3.
25 The basic goal of these studies is not only identify

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1 or define the toxicity profile and identify target
2 organs, but also to provide a basis for the
3 extrapolation of the animal data to humans.

4 To do this, we recommend the following
5 studies: Single and repeat dose toxicity studies in
6 a rodent and non-rodent species, the duration of which
7 is six to 12 months;

8 Pharmacokinetic and toxicokinetic studies
9 to be conducted at a minimum in the two species in
10 which the repeat dose toxicity studies were conducted;

11 Safety pharmacology studies to address the
12 potential toxicity to vital organs; reproductive
13 toxicology studies to address potential effects on
14 male and female fertility, embryo/fetal development,
15 teratogenicity and pre- and post-natal development;

16 genetic toxicity studies to address the
17 potential damage to genes or chromosomes -- this
18 includes both in vitro and in vivo assays; and

19 Finally, the carcinogenicity studies to
20 address potential tumorigenicity of a compound.

21 These are generally conducted in a mouse
22 and a rat. typically, they have been two-year
23 bioassays. More recently, they have been -- we have
24 been accepting transgenic models.

25 As I said, these are the general

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1 recommendations, but we make a determination of what
2 the recommendation will be on a case by case basis for
3 each drug. Because GL701 or DHEA is an endogenous
4 substance and because we do know that it is
5 metabolized to androgenic and estrogenic compounds or
6 metabolites, we modified our general approach.

7 Based on a number of discussions with the
8 sponsor and the Division, the sponsors agreed to
9 conduct a six-month repeat dose toxicity in dogs, and
10 this would include toxicokinetic endpoints. They
11 would conduct a standard battery of reproductive
12 toxicity studies, as well as a standard battery of
13 genotoxicity studies.

14 As part of the review process, we
15 requested an audit of two of the pivotal studies.
16 This audit identified significant deviations from Good
17 Laboratory Practices. However, I will comment that
18 the review is still ongoing, and a final resolution of
19 these issues and the impact on the studies has not
20 been determined.

21 With respect to the six-month repeat dose
22 dog study, the toxicities that we saw were generally
23 anticipated. The primary target organs were
24 reproductive organs.

25 In the female dogs, we observed

1 interruption of the estral cycle. This was
2 characterized by depletion of the tertiary follicles
3 as well as the development of cystic follicles in some
4 of the lower doses.

5 In the males we saw hypospermatogenesis.
6 The doses in the males were 1500 milligrams per
7 kilogram, and in the females we saw effects at ten
8 milligrams per kilogram and above, with a definite
9 dose dependent response.

10 There was also lipid depletion of the zona
11 reticularis. This again is because of the fact that
12 the zona reticularis is the site for synthesis of the
13 androgens and estrogens. It's not surprising.

14 With respect to liver, the effects were
15 not clear-cut. There was an increase -- When we look
16 at the individual animals and compare to their
17 baseline values, there was an increase in ALT.
18 However, there were no histopathological correlates
19 associated with that.

20 In a preliminary study in rats conducted
21 by the sponsor, as well as in the dog, we saw a
22 similar effect that we see in humans in that there is
23 a cholesterol lowering effect.

24 Again, the reproductive toxicity studies:
25 The findings were not unanticipated. These results

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1 refer to the rat. In the females there was an
2 interruption of the estrous cyclicity, and there was
3 also a decreased number of corpora lutea.

4 There was a decrease in embryofetal
5 viability. It was again a dose dependent response.
6 When we got up to doses around 160 milligrams per
7 kilogram, there was 100 percent reduction in the pup
8 viability.

9 There was increase in skeletal variations.
10 This was characterized by an increase in wavy ribs, as
11 well as delayed ossification, which suggests that
12 there is a delay in maturation.

13 In the pre- and post-natal development, we
14 saw similar findings with fetal toxicity. There was
15 an increase incidence in the number of dams that had
16 100 percent resorption, and there was also a decrease
17 in pup birth weight which persisted through the
18 lactation period.

19 With respect to the battery of genetic
20 toxicology studies that were conducted, it was
21 negative in the bacterial reverse mutation assay or
22 the Ames assay, and it was negative in the in vivo
23 mouse micronucleus assay.

24 It was positive in the in vitro Chinese
25 hamster ovary cell chromosomal aberration assay. I

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1 will add, though, that estrogen has been found to
2 induce chromosomal aberrations in both in vitro and in
3 vivo systems.

4 Now with respect to carcinogenicity, we
5 had a number of discussions about what would be the
6 most appropriate approach. Again, based on the fact
7 that we do know that GL701 is metabolized to androgens
8 and estrogens, and we do have a fair amount of data
9 available for that, we agreed to not recommending that
10 carcinogenicity studies were conducted prior to
11 submission of the NDA, and that we felt that it would
12 be appropriate to use the labeling for estrogens and
13 androgens as a basis for labeling prasterone.

14 There is a fair amount of literature,
15 nonclinical literature, available. But what you come
16 away with when you look at it is the fact that there
17 is -- when you're trying to analyze the activity of
18 DHEA with relation to carcinogenicity is that there is
19 not a single unifying hypothesis that can answer all
20 of the effects that we are seeing.

21 Depending on a number of variables, DHEA
22 has been shown to be both chemoprotective and
23 carcinogenic. It does look like some of the factors
24 have to do with the type of tumor model that you are
25 looking at, whether it's a spontaneous tumor, whether

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1 it's chemically induced, whether it's a transplanted
2 tumor, the hormonal status of the individual animal.
3 But there are a number of variables which can impact
4 this.

5 When we look at the hormone sensitive
6 tumors, again there is somewhat contradictory data out
7 there, being both inhibitory and stimulatory to these
8 types of tumors. In fact, what we see with breast
9 cancer cells, both in vitro and in vivo, when the
10 system has low estrogen -- either there is no estrogen
11 in the culture media or the animals have been
12 ovariectomized -- DHEA appears to be stimulatory.

13 On the other hand, if you add estrogen
14 into the culture media or the animal is intact, it can
15 be inhibitory to the carcinogenic effects.

16 What I think does become clear when we
17 look at the literature is that, when we are looking at
18 androgenic and estrogenic activity, DHEA is less
19 potent than its estrogen and androgenic metabolites.
20 I think this also pertains to other pharmacological
21 activity that we see as well.

22 As I said, we tried to define what the
23 activity in the mechanism of the activity with respect
24 to inhibition of tumor development. Again, I don't
25 think we can identify a single effect, and we have

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1 both hormonal and nonhormonal activity accounting for
2 it.

3 What the data do suggest is that DHEA, in
4 and of itself, does have some apparent activity for
5 inhibition that is separated from the hormonal
6 activity.

7 Now when we look at the data that
8 indicates carcinogenicity, we do observe
9 hepatocarcinogenicity in both the rat and the trout.
10 When we look at the rat, it is associated with
11 peroxisomal proliferation and, because of that, the
12 relevance to humans is definitely questionable.

13 When we look at the trout, what we do find
14 in the trout is a model that is very -- has been shown
15 to be very sensitive to a number of hepatic
16 carcinogens, and the one that comes to mind is
17 aflatoxin B, and that is not associated with
18 peroxisomal proliferation in the trout.

19 There is also a report describing the
20 increase incidence of granulosa cell tumors in
21 genetically predisposed mice.

22 Now when we look at the human literature,
23 again it doesn't answer the question conclusively.
24 There are some problems with the literature. There
25 are no randomized, well controlled trials.

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1 There are a number of anecdotal reports,
2 but a large majority of the trials that I saw -- what
3 they were looking at was endogenous levels of DHEA and
4 trying to correlate increases or decreases in the
5 endogenous levels to changes or increased risk of
6 cancer.

7 I think one thing that is accepted is that
8 there is a theoretical risk, but it is an unproven
9 risk. I think it is probable that it is going to be
10 very difficult to define the carcinogenic potential of
11 DHEA, as it has been with the estrogens and androgens.

12 Thank you.

13 ACTING CHAIRMAN HARRIS: Thank you.

14 DR. ADEBOWALE: Good morning, Chairman,
15 ladies and gentlemen. Basically, my presentation is
16 about dehydroepiandrosterone, DHEA, and cortisol
17 response.

18 The objective is to present the results of
19 adrenal function testing with Cortrosyn, which is
20 synthetic ACTH, stimulation following dosing of GL701
21 at a dose of 200 milligrams once daily for 28 days,
22 and this was based on a trial -- this was obtained
23 from trial GL96-02, which is a
24 pharmacokinetic/pharmacodynamic study.

25 The objectives of the trial GL96-02

1 basically were -- The primary objective was to assess
2 the interaction between DHEA and prednisone from a
3 pharmacokinetic and pharmacodynamic perspective, since
4 one of the possible benefits of GL701 is that it is
5 steroid sparing. So it was critical to rule out the
6 possibility of pharmacokinetic interaction with
7 prednisone.

8 Basically, the data did not -- suggested
9 that there was no pharmacokinetic or pharmacodynamic
10 interaction with prednisone, and between prednisone
11 and DHEA at the dose studied.

12 Another objective was to look at the
13 pharmacodynamic response to DHEA, and this was
14 assessed by adrenal function testing with Cortrosyn in
15 the absence of prednisone.

16 If we talk about the methods, like I said,
17 this was a Phase I trial -- 96-02 is a Phase I
18 crossover trial in 14 pre-menopausal healthy women to
19 evaluate the effect of 28 days oral administration of
20 GL701 200 milligrams per day on single dose
21 pharmacokinetics of orally administered prednisone.

22 The ACTH stimulation test, the
23 pharmacodynamic response was evaluated in this trial
24 by administering 250 micrograms of synthetic ACTH as
25 an IV bolus pre- and post-28 days following GL701

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1 administration.

2 The applicant defined the plasma cortisol
3 concentration that will be indicative of normal
4 adrenal function as greater than or equal to 200
5 nanograms per mil at one hour post-ACTH injection.

6 On the next table are represented the mean
7 plasma cortisol levels, and baseline Day Zero refers
8 to pre-administration of DHEA, and Day 28 refers to
9 the plasma cortisol levels after 28 days
10 administration of DHEA, and the pre-Cortrosyn is
11 before the eighth day stimulation test.

12 As you can see, the levels before ACTH
13 injection on Day Zero and Day 28 -- the mean levels
14 are 68.3 and 66.8 nanograms per mil, and this
15 difference was not found to be statistically
16 significant. However, post-Cortrosyn after one hour -
17 - one hour after the ACTH injection, the plasma
18 cortisol levels on Day Zero were 233.5 nanograms per
19 mil, and on Day 28, which is 28 days after DHEA
20 administration, were 210 nanograms per mil.

21 So, you have a slight decrease in the
22 plasma cortisol levels 28 days after DHEA
23 administration, and this was found to be - this
24 difference between Day Zero and Day 28 post-ACTH in
25 the cortisol levels was found to be statistically

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1 significant. However, note that the plasma cortisol
2 levels post-Cortrosyn are actually higher than the 200
3 nanograms per mil that was predefined by the applicant
4 as indicative of normal adrenal function.

5 The next slide we have the stick plots of
6 the individual data. Basically, in this stick plot
7 the red line indicates the 200 nanogram per mil plasma
8 cortisol concentration level, which is indicative of
9 normal adrenal function, as defined by the applicant.

10 These are the baseline cortisol
11 concentrations at Day Zero before any DHEA was
12 administered to the subjects. When we look at these
13 stick plots, we see that there are two patients,
14 basically, that actually had cortisol levels -- I mean
15 that had cortisol levels that increased to levels
16 below the 200 nanograms per mil after the ACTH
17 injection, but most levels had -- most subjects had
18 levels that were greater than 200 nanograms per mil
19 post-ACTH.

20 The same thing when we look at the stick
21 plots for the plasma cortisol concentrations post-ACTH
22 after administering DHEA for 28 days. You also see
23 that you get that increase from pre-ACTH to post-ACTH.
24 However, you had three subjects who had levels below
25 the 200 nanograms per mil, indicative of normal

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1 adrenal function.

2 In the next graph we compare the plasma
3 cortisol concentrations before the ACTH stimulation on
4 Day Zero and Day 28. Basically, when we look at both
5 -- when we look at these stick plots, we see that
6 before ACTH stimulation on Day Zero and Day 28, you
7 had variable responses, but the medians were very
8 similar, and so was the mean. But the cortisol
9 concentrations were variable for both groups.
10 However, when we look at plasma concentrations after
11 ACTH stimulation on Day Zero and Day 28, when we look
12 at Day Zero post-ACTH, we find that the median was
13 about 236 nanograms. But what is more dramatic in
14 this graph is that after 28 days post-ACTH most of the
15 cortisol concentrations -- you saw somewhat of a trend
16 in that you got decreases for most of the subjects
17 except about three subjects, but the median was still,
18 you know, very similar and above the cortisol
19 concentration levels, indicative of normal adrenal
20 function. But this graph shows you somewhat of a
21 trend, that you get some kind of a decrease, which
22 probably suggests some blunting to the response to the
23 adrenal glands.

24 So, basically, in summary or conclusions,
25 the mean plasma cortisol concentrations following 28

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1 days of DHEA were greater than 200 nanograms per mil
2 in all but three subjects, two who had levels of
3 cortisol less than 200 nanograms per mil at baseline
4 following ACTH stimulation. However, a small but
5 statistically significant reduction in plasma cortisol
6 concentrations was seen after 28 days of DHEA 200
7 milligrams per day.

8 So these results raise the possibility
9 that DHEA or one of its metabolites may have a mild
10 glucocorticoid-like activity. However, the long term
11 impact of this effect is unknown. Thank you.

12 ACTING CHAIRMAN HARRIS: Thank you. Dr.
13 Johnson?

14 DR. JOHNSON: Thank you very much, Mr.
15 Chairman. I am going to make a few introductory
16 comments again before I get into my review itself.

17 We've heard a lot of interesting
18 discussion already today, and I'm hoping this
19 afternoon will blossom forth in a useful manner. I
20 think what Dr. Hurley mentioned is important, that in
21 the end what we are looking for is scientific validity
22 here, and that means, as sort of a backdrop, we are
23 going to be -- there's a backdrop of the whole arena
24 of the principles of trial design and analysis.

25 These things would even trump an FDA

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1 document, if one existed, but we don't have one at
2 this point for lupus, as has been pointed out by a
3 number of people.

4 Secondly, this issue of uncharted
5 territory can't be overemphasized, obviously. This
6 was a collaborative process from the outset, and a
7 challenging one, and we all anticipated that.

8 There were certain decisions that I think
9 we did make at the protocol development time that I
10 will comment on in my talk. The territory being
11 uncharted is not a problem.

12 If you clearly succeed, then you say your
13 drug worked and your methodology worked. If the
14 conclusions don't look overwhelming, then the question
15 always comes up, is this a methodologic problem or is
16 it a drug problem or a combination of the two.

17 Sometimes tough methodologic questions can
18 themselves be addressed in pilot studies. That really
19 wasn't the case here. There was a pilot study from
20 Stanford that did use the SLEDAI as one of its
21 measurements, but the innovations that were worked on
22 here -- and Murray gave them a very positive spin; I
23 hope these were positive innovations -- had not been
24 used before in RCTs.

25 So, you know, when all of the verbiage is

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1 set aside, I think the goal here is to have the
2 Committee, having been familiarized with the protocols
3 themselves and to see the data laid out and then just
4 let the discussion move forward.

5 The inferential implications of the data
6 are one aspect of things, but the scientific
7 understanding of the data is another goal here.

8 Now the outline of my talk will follow as
9 you see here. I am going to concentrate on 94-01 and
10 95-02 and make some comments on their designs and the
11 populations that were entered in these trials. We
12 have already had some discussion.

13 When I clearly overlap with the sponsor,
14 I will just roll through the slides, to save time.
15 Then I will go over the efficacy results for the two
16 trials, and then some discussion of this SLEDAI greater
17 than 2 signal, and then a few comments at the end
18 about safety.

19 94-01, the steroid sparing design: Again,
20 there are a few precedents. There are a couple of
21 precedents outside of rheumatology, but not within
22 lupus, obviously. It's an interesting endpoint in the
23 sense that you are not actually measuring the direct
24 impact of the drug's effect on the patient, but you
25 are measuring, in this case, the mandated requirement

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1 for the physician to change the medications based on
2 those assessments that the drug impacts.

3 So it's sort of -- a bit more of a
4 downstream measure, and I think that, in and of
5 itself, probably injects more variability and, thus,
6 uncertainty when you use something like this as a
7 design maneuver.

8 Secondly, you have heard some discussion
9 already about the steroid-stuck patients, so called.
10 We had a lot of discussion about this, I think, with
11 the very full realization that these are very
12 difficult to define.

13 We finally came up with these two
14 different -- two roots by which patients could enroll
15 in the trial that you have heard of. There's always
16 sort of a balance of an attempt to facilitate accrual
17 versus trying to get, you know, precisely the right
18 kind of patient you want in a trial who is very
19 responsive.

20 As has been mentioned before, the whole
21 sort of face validity of steroid sparing was not
22 really particularly contentious. That, in theory, was
23 a very attractive goal for our clinical trial in
24 lupus.

25 You have heard about the two primary

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1 endpoints. I put it in quotes here. The first one
2 was, as somebody pointed out -- Dr. Strand pointed out
3 -- it, obviously, was a more clinically demanding
4 endpoint. But it wasn't considered an essential one,
5 and by that I mean this was an endpoint that was
6 construed to enable the sponsor to attain Subpart E
7 status, and it had to be a clinically important
8 endpoint.

9 It is what I call durable reduction in
10 steroids, and by durable I mean it had to have lasted
11 for the entirety of the trial, because as you recall,
12 Michelle mentioned this, that this particular endpoint
13 had to get you down to steroids at 7.5 a day for at
14 least a two month period of time, and that two-month
15 period of time had to capture the end of the trial,
16 which was variably seven to nine months.

17 For the statisticians in the crowd, there
18 wasn't any alpha cost for this Subpart E endpoint.

19 The second endpoint we will want to
20 further discuss. This, at least potentially, you
21 would think, at least theoretically, would be a more
22 sensitive endpoint if it was a valid endpoint. Again,
23 it hadn't been used in a lot of trials, and it was
24 defined as the mean change in the prednisone dose
25 itself.

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1 Now here is the timeline for this trial.
2 It started in '94, mid-'94, and the last patient
3 finished about two years later. There was various
4 cleaning up of the database and so on. That's pretty
5 routine. That led eventually to the blind being
6 broken almost a year later.

7 During this process before the arms were
8 identified, as you have heard from the sponsor, there
9 was this -- it was discovered that the response rates
10 for the low SLEDAI patients were a lot higher, in the
11 sixties and seventy percent range, compared to the
12 other larger SLEDAI categories.

13 So this trial itself had an amendment
14 which added baseline SLEDAI to the covariates. There
15 was a structure in the protocol that specified a
16 number of possible covariates and the test that they
17 would have to pass in order for them to become an
18 actual covariate for the primary analysis, which
19 wasn't simply a comparison of proportions; because
20 there was the desire to have the ability to
21 incorporate covariates, and to do that you needed to
22 fall back to something like a logistic regression
23 model.

24 Now here -- You have seen most of this
25 information from Dr. Petri's presentation already.

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1 Baseline prednisone had to be between 10 to 30 to get
2 in, and turned out to be 13, 13, and 15. This was not
3 imbalanced, as you have heard discussed. It turned
4 out that it was imbalanced when you went to the SLEDAI
5 grid of n 2 subset, which will become a point of
6 interest later on.

7 The entry SLEDAI, interestingly, were in
8 the 6 range, as were the entry SLEDAI for the second
9 trial, as it turns out.

10 Here are the withdrawals divided into
11 inefficacy and adverse events. These are the standard
12 categories, and these are log rank P values showing no
13 statistical difference here.

14 It's always tempting in these trials to go
15 back and sort of, you know, reassign these patients,
16 and I have done this in the past. I think that is
17 risky in some sense, because you are sort of arguing
18 that you can trump the primary investigator.

19 In any case, if you -- There is a lot of
20 uncertainty, I'm sure, about a lot of these particular
21 calls, but if you are going to draw any inferential
22 conclusions from any of these analyses, then you sort
23 of fall back to the argument, well, you've got a
24 controlled trial or you've got another arm that should
25 balance out any kind of defect that occurs in one arm,

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1 at least in theory, if the trial is big enough.

2 Here are the results from the first trial.
3 The first primary endpoint, this notion of attaining
4 a durable prednisone -- physiologic prednisone dose
5 out to the end of the trial. GL701, 200 milligrams,
6 55 percent; 100 milligrams, 44 percent; placebo, 41
7 percent. Here are the P values.

8 The second primary endpoint, the percent
9 change in prednisone presented either by median or
10 means: There were some outliers which don't affect
11 the median as much as they do the mean here.

12 If you now probe the data in light of the
13 hypothesis that the SLEDAI greater than 2 are a more
14 responsive subset, the question is what do you get?
15 Again by achieving durable prednisone, the comparison
16 of GL701 versus placebo is .18 in 100 milligrams
17 versus placebo is .75.

18 Now as I mentioned a few minutes ago, it
19 turned out that in the SLEDAI greater than 2 subset
20 there was a statistically significant imbalance of
21 prednisone. So this figure -- These analyses assume,
22 as per protocol, that that covariate was included in
23 the logistic regression analysis. If you don't --
24 which is what the asterisk down here says -- If you
25 don't adjust for anything, you just do an unadjusted

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1 analysis, you get the 0.031 value.

2 Here is the mean change in prednisone,
3 again for this SLEDAI greater than 2 subset. This got
4 a little mismatched on the slide. This column here
5 are the mean values, and this column here are the
6 median values. So these actually flow pretty
7 similarly to the values that you saw for the entire
8 randomized set in this trial.

9 Okay. Again, a little more exploration of
10 the data here, according to SLEDAI subsets. These
11 were just an arbitrary cut that I made, 0-1, 2-4, 4-8,
12 and greater than 8. There, obviously, would be other
13 ways to cut up the SLEDAI, if you so chose.

14 It turned out that the numbers, if you
15 look at the denominators -- Well, the numbers are
16 small throughout here. So I'm not sure how one would
17 interpret this. I just put it up here for your
18 information.

19 Of the original 63 and 64 patients, they
20 are distributed according to the denominators, and the
21 numerators here are the numbers who responded. Again,
22 this is the achieving durable physiological dose
23 steroids as the measure of response.

24 This is the mean change of prednisone from
25 baseline, again broken out by SLEDAI at baseline. So

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1 these are all percent values. Again, I just put these
2 up here for descriptive purposes, not really knowing
3 how to further interpret them.

4 Now I would like to move on to the second
5 trial, 95-02. This, as you know now, is a by-patient
6 -- used a by-patient, dichotomous endpoint, but again
7 it didn't simply compare proportions but used a little
8 more sophisticated logistic regression model, so that
9 covariates could be incorporated.

10 As you have heard, the endpoint here was
11 designed to capture the totality of drug effects, and
12 we really don't have a precedent of using an endpoint
13 like this in lupus. Prednisone was fixed with very
14 little exception in this trial, which is completely
15 different. I mean, the goal of the first trial was to
16 unfix the prednisone, because every time your SLEDAI
17 was stable, you had to drop the steroids.

18 You know, this was a more traditional
19 trial, and everything was supposedly fixed, and you
20 impose your intervention in one arm and your placebo
21 in the other arm, and you watch for a change.

22 It's important to note that this trial was
23 designed and actually started before the other trial
24 was done.

25 Now a few comments on the primary endpoint

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1 in trial 95-02, this so called responder index. As
2 you have heard, we had hours and hours of discussion
3 about trying to conceptualize what we thought would be
4 a robust instrument in the absence of any priors for
5 lupus RCTs.

6 There was nervousness about simply using
7 one activity measure. So we used two. There was
8 nervousness about using one measure to capture what
9 the instruments didn't capture well, which was sort of
10 fatigue and sort of feeling lousy, these sort of
11 constitutional symptoms that sometimes dominate the
12 picture in lupus. Accordingly, the decision was made
13 to use two measures to capture that, too, the Krupp
14 Fatigue Scale and the patient global.

15 You know, there was some flavor of quality
16 of life to this. I must say, I don't think it was
17 fully an attempt to capture quality of life. Quality
18 of life itself is sort of a challenging concept, and
19 it was one of the domains that OMERACT felt should be
20 measured in all lupus trials.

21 I'm not quite sure we really -- I almost
22 got the sense from listening to Murray's talk that we
23 had achieved what OMERACT couldn't quite accomplish in
24 activity and damage and quality of life and drug
25 toxicity. But we did try to address those things in

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1 this endpoint, because we wanted the debate to be up
2 front in the design and not after the analysis.

3 So in any case, the whole damage dimension
4 of things was not -- Actually, the SLICs were measured
5 throughout this trial, and that data is interesting,
6 in and of itself, but damage in a major way we tried
7 to capture in a whole list of items that I thought
8 would be presented this morning but wasn't. So I will
9 go over those briefly.

10 We had a whole list of things that we
11 didn't want to allow to occur and have the patient be
12 considered a success. Okay? As Matt had pointed out
13 earlier, a lot of things can happen with these scales.
14 You could actually have a CVA and, if enough other
15 things in your SLEDAI or your SLAM have improved, then
16 your total scale will improve.

17 So we had a whole list of items that was
18 pretty broad agreement represented a major clinical
19 deterioration due to lupus or due to drug effects
20 that should invalidate a patient being classified as
21 a responder, if he was otherwise classified.

22 I'm going to just read these off to you.
23 I don't have a slide, but they are in my review, and
24 I think they are the sponsor's material, too: New-
25 onset diabetes that was defined in a pretty robust

1 fashion; a new ulcer requiring hospitalization or
2 transfusion; new-onset hypertension requiring therapy
3 for at least three months; myocardial infarction; new
4 steroid myopathy; a new major bump in transaminases;
5 new osteoporotic fracture; a whole collection of CNS
6 events including stroke and transverse myelitis and so
7 on; a nuance that seizures refractory to therapy;
8 renal failure or progression to dialysis; new or
9 worsened pulmonary hypertension or interstitial lung
10 disease; refractory pericarditis; ischemic bowel
11 disease requiring resection; vasculitis resulting in
12 infarct; thrombocytopenia resulting in significant
13 hemorrhage with sequelae; persistent leukopenia
14 resulting in recurrent infections for three months;
15 and any increase in concomitant methotrexate
16 azathioprine or a new cytotoxic therapy during or six
17 weeks post-discontinuation or any prednisone increase
18 beyond limits in the protocols.

19 So you can see that the spirit behind all
20 this was to try to capture these sort of bad news
21 events. And interestingly, it turned out that exactly
22 the same number of patients in each arm of this trial,
23 in fact, experienced one of those events. I think
24 there were 16 patients in both arms.

25 Now the issue of where the cutoff is for

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1 these measures was also discussed, and we went round
2 and round on this, because, obviously, we were aware
3 at the time that these measures were variable and
4 probably more variable than measures in rheumatoid
5 arthritis, for that matter.

6 It was agreed in the end that you have to
7 draw a line somewhere. You are going to draw a line
8 in the sand, and anything above that is going to win,
9 and anything below that is going to lose. Just for
10 simplicity's sake, we called that cutoff the zero
11 cutoff itself, and we didn't say it was five percent
12 less than zero or five percent above zero.

13 The protocol says something like
14 improvement or stabilization. So any deterioration by
15 any one of these measures made you a nonresponder.

16 There was concern, I must say, you know,
17 given that there were no precedents here, that we
18 might be construing an endpoint that would really get
19 us into trouble in the sense that it would be much too
20 rare or much too common. And if you are one extreme
21 or the other of sort of that S-shape response curve
22 that Frank showed before, you lose your statistical
23 power.

24 So if the endpoint had turned out to have
25 a 90 and a 95 percent hit rate in the two arms

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1 respectively or a 2.5 and a 5 percent rate in the arms
2 respectively, then we would have been in trouble, and
3 we would have had to have considered some sort of
4 fall-back analysis. But that didn't happen. However
5 you define the cutoff, you are sort of in the middle
6 of the curves here.

7 Now 95-02, the timelines like I did for
8 the first trial: Started in March '96 and finished
9 three years later. There were a number of amendments
10 to this trial. You have heard about the amendment
11 that was prompted by the findings from the first
12 trial, which appropriately wanted to bump up the power
13 of this trial by enrolling more patients and, in
14 addition, having these patients at least be required
15 to have a SLEDAI greater than 2 for entry.

16 There was the finding that you saw in one
17 of Michelle's slides, I believe, that post-menopausal
18 patients on DHEA who were not on hormone replacement
19 therapy tended to have their estrogen levels bump back
20 up to the pre-menopausal state, and thus the concern
21 of unopposed exposure by uterus or breast. So a
22 monitoring program was put in place for these patients
23 to follow uterine ultrasounds and mammograms for post-
24 menopausal patients.

25 Finally, there was a prolonged discussion

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1 over a couple of years to try to finalize this
2 statistical analysis plan. This started out as a
3 desire to modify the population -- in light of the
4 first study, to modify the population for analysis to
5 include only the SLEDAI greater than 2 patients.

6 There was then added a modified responder
7 definition that you have heard about, the so called
8 window concept. finally, there was a proposal to
9 modify the population to be analyzed, requiring
10 patients to have been on therapy for 60 days. This
11 statistical analysis plan was -- the final version of
12 it -- was submitted on April 30, 1999.

13 Okay. Here are the patients from 95-02.
14 Note the mean prednisone dose is quite low in this
15 trial. That was by intent. Cytotoxics were allowed
16 here, and about a sixth of the patients were on
17 cytotoxic agents, stable cytotoxic agents.
18 Interestingly, the SLEDAIs are still about the same on
19 average, although the range is broad.

20 Here is the same survival analyses by log
21 rank P test for this trial as I showed you for the
22 first trial. There was a P value of .04 reached here
23 because of adverse event withdrawals, again dominated
24 by hirsutism and acne. All cause withdrawals trended
25 in favor -- trended to be more all cause withdrawals

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1 due to GL701 versus placebo.

2 Okay. Here are the all randomized, the
3 primary analysis, the first endpoint, the number of
4 responders. You recall, those are the patients who
5 met all four - who didn't deteriorate by any of those
6 four parameters, the SLEDAI, the SLAM, the KFSS or the
7 patient VAS, and had none of those clinical
8 deterioration features.

9 This is a logistic regression model with
10 inclusion of whatever covariates were pre-specified in
11 the protocol, and the P value here is .436, 31 percent
12 versus 27 percent.

13 There were a number of secondary analyses,
14 some of which I am going to show here. The mean
15 change in the four parameters that were used and the
16 investigator, global, SF-36 all showed P values of .25
17 or greater. I'll list a few of those on the next
18 slide.

19 Another pre-specified secondary analysis
20 was all cause, the time to withdrawal by the log rank
21 test which, as I showed you in a previous slide,
22 showed a P of .80 trend in favor of placebo.

23 These are the mean differences across the
24 trial in these four variables GL701 versus placebo and
25 the respective P values. I didn't put in the standard

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1 deviations here to reflect the variability.

2 If you now go from -- The original cohort
3 was 380 or thereabouts. If you go down to the cohort
4 of 293 patients, if you look at the SLEDAI greater
5 than 2 subset in this trial and look at the number of
6 responders, you've got 55 over 147 on GL702 versus 42
7 over 146, which is a P of .127.

8 If you look at the secondary measures,
9 secondary outcomes, mean change in these outcomes
10 again across the two arms, these are the P values you
11 get.

12 If you now go to a smaller subset here --
13 we are now down to 265 patients, and this is the --
14 These are patients who fulfilled two criteria. One is
15 that their baseline SLEDAI was more than 2 and,
16 secondly, they have been exposed to at least 60 days
17 of therapy. The values you get are 56 over 132 and 42
18 over 133. So there is a numerical difference there.
19 The P value is .068.

20 A few more slides. If you use this same
21 subset of 265 patients, but you use the modified
22 window that you heard about, then you are up to 87
23 responders in the drug arm versus 65 in placebo, which
24 is a .005 P value.

25 So here is a summary of these various

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1 results, starting up here with all patients, 381, the
2 greater than 60 day subset which is at 346 patient
3 subset, the SLEDAI greater than 2 subset which is 293,
4 and the subset that fulfills both these criteria, 60
5 days of therapy and SLEDAI greater than 2, 268.

6 Then finally, this particular cohort, 265
7 patients, using the new window is the P value of .0005
8 here.

9 So let me conclude with a few slides. You
10 have heard some discussion, and I'm sure there will be
11 more this afternoon, about various safety dimensions
12 of this database. It's an interesting database.

13 Some of it is very anticipated on a
14 physiologic basis. There was a signal for abdominal
15 pain in the first trial which didn't bear out in the
16 second trial, and then there's a question of whether
17 or not there's renal signal.

18 The analysis that Michelle referred to
19 this morning, I'm not sure everybody knows what I did.
20 So I'm not sure she could appreciate what she was
21 responding to or if the audience could appreciate what
22 she was responding to.

23 What I simply did was go through the
24 patients who had, by certain pre-defined criteria,
25 new-onset -- new or worsening hematuria, proteinuria,

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1 fall in complement levels, or rising DNA levels, and
2 simply do a count of the number of patients who had
3 one of those items.

4 Then I did a count of the number of
5 patients who had two or more of those items. I'm not
6 going to belabor those results, because it's an
7 exploratory analysis, but there was a trend that
8 favored placebo.

9 So you know, the question comes up, What
10 is going on here? I think this clearly needs further
11 explanation, and this, I think, is going to need to be
12 further addressed in some kind of setting where maybe
13 there is a dedicated lab that deals with the assay
14 variability that's a big problem with some of these
15 renal parameters.

16 Finally, you have heard -- and I'm going
17 to show a slide or two on adverse events themselves,
18 but it's not going to add very much to what you have
19 already heard. As a background in the entire safety
20 discussion are these concerns about chronic exposure
21 that you have heard from Dr. Wilson and what may or
22 may not be the long term consequences of lipid
23 alterations.

24 I've broken down my -- I have two slides
25 on adverse events. I didn't combine them together

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1 like Michelle did. But again it shows the sort of
2 things you anticipate. Acne had significantly more
3 events, hit rates in the two drug arms versus placebo.

4 Here is the abdominal pain signal I
5 mentioned to you from the first trial. There was a
6 hypertension signal by this methodology that we did
7 look at closely, and we couldn't convince ourselves
8 that this was real. Then there was more stomatitis,
9 for some reason, in this arm versus placebo.

10 Then placebo dominated for two events
11 here, lupus LE rash and sinusitis. These six items
12 here weren't cherry-picked. These were just simply
13 taken out of a long list for the ones that did show a
14 statistically significant greater event rate than one
15 arm versus the other. That's how this table was
16 constructed.

17 Here's the same table for 95-02, again
18 showing acne and hirsutism in association with GL701,
19 and this time stomatitis is more common in placebo,
20 which you would expect if you are presuming a drug
21 effect here, and myalgia was more common in placebo.

22 So in conclusion, there's a lot of things
23 for the Committee to discuss this afternoon. I just
24 summarized some of what seemed to me to be the
25 outstanding issues regarding the weight of evidence

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1 here.

2 One is, you know, the consistency of the
3 results across endpoints and across trials. The
4 second is how would you weigh analyses of withdrawals
5 as a method to balance safety and efficacy? Finally
6 and maybe most importantly here, which analyses rise,
7 on clinical grounds, to a level of importance here?

8 ACTING CHAIRMAN HARRIS: Thank you very
9 much. Dr. Lu.

10 DR. LU: I am going to talk about
11 statistical issues in this NDA. First, I am going to
12 discuss the ITT versus per-protocol analyses in study
13 95-02. I will also talk about the definitions for a
14 responder in study 95-02, including the original
15 definition, the window definition proposed by sponsor.
16 I will also present the results of window sensitivity
17 analysis. finally, I will discuss subgroup analysis
18 in patients with baseline SLEDAI larger than 2.

19 The ITT population was specified in the
20 original protocol. It included all randomized
21 patients. The per-protocol analysis was proposed in
22 a later submitted statistical plan where most patients
23 had finished study. It excluded dropouts within the
24 first 60 days.

25 ITT analysis preserves randomization,

1 which is the base for valid statistical inference. In
2 general, it avoids over-estimation of treatment
3 effect.

4 The sponsor's reason for per-protocol
5 analysis is that treatment needs at least 60 days to
6 take into effect. To assess the validity of the per-
7 protocol analysis, we look at the patient disposition
8 among the patients excluded from the ITT population.

9 In the placebo group, a total of 16
10 patients were excluded, among them three dropouts due
11 to treatment related adverse events. In the DHEA
12 group, a total of 19 patients dropped out -- I'm
13 sorry, excluded from the ITT population. One of them
14 was due to lack of efficacy, and eight of them were
15 due to treatment related adverse events.

16 So there are treatment related dropouts,
17 especially in the DHEA group. About 50 percent of the
18 patients dropped out due to either lack of efficacy or
19 ARE. This table is derived from the sponsor's data.

20 So excluding early dropouts in the per-
21 protocol analysis may bias conclusion, since there are
22 treatment related dropouts.

23 Now I am going to discuss the definitions
24 for responder in study 95-02. The original definition
25 for responder needs two requirements. The first one

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1 is improvement or stabilization in SLAM, SLEDAI,
2 Fatigue Score and Patient VAS.

3 Specifically, improvement or stabilization
4 were characterized as, for each score, post-baseline
5 weighted average no worse than the baseline score.

6 The second requirement is no clinical
7 deterioration. Based on the original definition in
8 the ITT population, the responder rate in the placebo
9 group is 27 percent. In the DHEA 200 milligram group,
10 it is 31 group, and the P value is .4378. So there is
11 no statistical significance demonstrated.

12 In the later submitted statistical
13 analysis plan the sponsor proposed a window
14 definition. The first requirement for a responder is
15 changed to: Compared with baseline, post-baseline
16 weighted average for SLAM should be no worse than 1,
17 for SLEDAI no worse than .5, for the Fatigue Score no
18 worse than .5, for patient VAS no worse than 10. The
19 second requirement remains the same.

20 This set of margin was selected by the
21 sponsor to represent variation in the baseline measure
22 as a tolerance window for stabilization of disease
23 activity. However, it is of interest to see how the
24 responder rate changed, allowing a range of margins.

25 To do that, we defined the window margin

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1 by percent of change from baseline. For example, an
2 active five percent window definition for a responder
3 is weighted average for each of SLAM, SLEDAI, Fatigue
4 Score, and Patient VAS should be no worse than five
5 percent from the baseline. The second requirement is
6 the same.

7 In this actually you see a similar plot
8 from Dr. Hurley. He gave the graph for the subgroup
9 with baseline SLEDAI larger than 2. Here I gave the
10 graph for the overall ITT patients. However, the
11 overall patterns are similar between the two graphs.

12 The X axis is the percent used for window
13 criteria. The y axis is the responder rate. The red
14 line with symbol 1 is for DHEA group. The black line
15 with symbol 0 is for the placebo group.

16 When the percent is zero, that corresponds
17 to the original definition. If worsening is allowed,
18 namely when the percentage is negative, DHEA group
19 shows numerical advantage over placebo. If you need
20 some improvement for the responder definition, then
21 the numerical advantage is lost. DHEA could even be --
22 has less responder rate than placebo.

23 So the numerical trend of responder rates
24 in treatment group is sensitive to whether worsening
25 is allowed in the responder definition.

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1 Now I am going to talk about subgroup
2 analysis in patients with baseline SLEDAI larger than
3 2. This subgroup analysis was conducted in both
4 studies. The result in this subgroup analysis was
5 used in the first study as hypothesis generating, and
6 the subgroup analysis was specified in the second
7 study in a protocol amendment.

8 Now let's look at the result in the first
9 study. The first primary endpoint is responder rate.
10 In the baseline SLEDAI less or equal to 2 group, the
11 responder rate in placebo group is 68 percent. In
12 DHEA 100 milligram group it is 63 percent. In DHEA
13 200 milligram group, it is 63 percent.

14 In the baseline SLEDAI larger than 2
15 group, the responder rate for placebo is 29 percent.
16 In DHEA 100 milligram, it is 38 percent, and DHEA 200
17 milligram is 51 percent. So in the baseline SLEDAI
18 larger than 2 group, there is a trend favoring the
19 DHEA groups, but in the baseline SLEDAI less or equal
20 to 2 group, the rates were comparable.

21 Let's look at the percent change from
22 baseline in prednisone dose in this baseline SLEDAI
23 larger than 2 group. The pre-specified primary
24 endpoint is mean percent change. In terms of mean,
25 the percent reduction for placebo group is 26 percent.

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1 For DHEA 100 milligram it is zero percent. for DHEA
2 200 milligram it is 22 percent.

3 I also tabulated the median here. For
4 placebo it is 33 percent reduction. For DHEA 100
5 milligram it is 33 percent reduction, and for DHEA 200
6 milligram group it is 50 percent reduction.

7 The different trend you have seen here is
8 due to the skewed data distribution, although it is
9 the validity of doing a rank analysis after we see the
10 data is questionable. However, if we do a Wilcoxin
11 test for the percent reduction of prednisone dose and
12 we first compare the 100 milligram versus placebo, the
13 mean rank score for the 100 milligram group is 48, and
14 for placebo is 44, and the P value is 1. Here a
15 higher mean rank score means less reduction.

16 When we compare DHEA 200 milligram with
17 placebo, the mean rank score for the 200 milligram is
18 44. For placebo it is 47, and the P value is .61. so
19 there is no separation between the DHEA and placebo
20 groups.

21 Now let's look at results in study 95-02.
22 The primary endpoint is responder rate. Here I am
23 showing you the result in the original definition
24 among the ITT population.

25 In the baseline SLEDAI less or equal than

1 2 group, the responder rate for placebo is 21 percent.
2 The responder rate for the DHEA 200 milligram is 7
3 percent. So the responder rate in the placebo group
4 is higher than that in the DHEA group.

5 In the baseline SLEDAI larger than 2
6 group, the responder rate for placebo is 29 percent.
7 For DHEA 200 milligram group it is 37 percent. So
8 DHEA has higher responder rate in this subgroup, and
9 overall there is a statistically significant
10 interaction by treatment -- by baseline SLEDAI.

11 So in summary, in study 94-01 the results
12 of primary endpoints were not consistent in baseline
13 SLEDAI larger than 2 group, because there is numerical
14 advantage in responder rate for DHEA, but no advantage
15 in mean percent change in prednisone dose was shown in
16 the DHEA group.

17 In study 95-02 DHEA showed numerical
18 advantage over placebo in responder rate in patients
19 with baseline SLEDAI larger than 2. Statistical
20 significance was not demonstrated by ITT analysis
21 without window. The P value is .17. A small P-value
22 of .005 was found by per-protocol analysis with a
23 window definition.

24 So overviewing the results in the first
25 study, which generated the hypothesis for the

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1 subgroup, and the results in the second study, we
2 raise the question: Are additional studies needed for
3 the baseline SLEDAI larger than 2 group to support an
4 efficacy claim? Thank you.

5 ACTING CHAIRMAN HARRIS: Thank you very
6 much, Dr. Lu.

7 Are there any questions with respect to
8 clarification? Dr. Anderson?

9 DR. ANDERSON: I have a question about the
10 modifications to the statistical analysis. It was --
11 Dr. Johnson said that they were submitted, but were
12 they accepted by the FDA, all of them or none of them
13 or just some?

14 DR. JOHNSON: Well, our philosophy was
15 that the primary analysis should remain unchanged,
16 that the protocol specified primary analysis should
17 remain -- has to remain unchanged to maintain
18 scientific viability, and that these other analyses
19 would be secondary analyses.

20 ACTING CHAIRMAN HARRIS: Can I press on
21 that some more? Was there a tacit understanding that
22 there might be -- these changes might be accepted?

23 DR. JOHNSON; No. No, but there is always
24 the tacit understanding that, if you don't quite make
25 it by your primary and all the totality of the data is

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1 strongly positive, that that secondary data could have
2 evidentiary weight. Does that make sense?

3 We wouldn't ignore the results of
4 secondary analyses.

5 ACTING CHAIRMAN HARRIS: In other words,
6 you felt that the secondary analysis might be
7 sufficient perhaps where one is in question, but it
8 might be sufficient to sway us one way or another?

9 DR. JOHNSON: Yes. That's probably a fair
10 interpretation.

11 ACTING CHAIRMAN HARRIS: Dr. Liang.

12 DR. LIANG: This is a comment. I think
13 that there are methodologists in this group, and I
14 think that a lot of our speech is about how, you know,
15 the classic books would tell us to do trials and to
16 explore the data, and that we skew polling the data
17 and what-not. But I have to remind the group, I
18 think, that the book has not been written on lupus,
19 even in terms of the metrics, the approach.

20 I think this is a -- For me, this is one
21 of the most exciting meetings I've been to, because I
22 think that we have really fine investigators who were
23 forging new territory. They made decisions, somewhat
24 supported by people in this room, at various times,
25 and they lived with it, and we are learning a lot

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1 about it.

2 We are really -- This is a really
3 meaningful discussion, because we are trying to
4 balance off being a hard-hat methodologist versus, you
5 know, understanding that we are seeing data that we've
6 never seen before from measures that we have never
7 used before.

8 DR. JOHNSON: Yes. I think all of us
9 would agree entirely with that sentiment, and that we
10 feel the same, and that we have felt the same all the
11 way through for the past eight years.

12 DR. LIANG: A lot of the stuff that I
13 could say as well about how it should be done, I would
14 just sort of bite my tongue and just take us where the
15 data takes us.

16 I am, however -- You know, frequently the
17 situation for other kinds of stuff I do, I think one
18 of the more problems is that we are seeing a lot of
19 data reduction and summaries. I think we would be
20 more comfortable if we saw, you know, the kind of
21 things that the other guy reviewed; because sometimes,
22 you know, the aggregation really hides the meaningful
23 stuff. I'd like to have an opportunity to do that
24 someday.

25 ACTING CHAIRMAN HARRIS: We will have the

1 excitement this afternoon, Dr. Liang. Dr. Silverman.

2 DR. SILVERMAN: I have a quick question.
3 When I looked at this trial design, I was just
4 wondering why the 90-day first visit was chosen. I
5 mean, we are all new -- It was 60? It was 90.

6 We are used to RA, JRA trials and,
7 unfortunately, we lost a lot of patients who never had
8 their first visit. Just what was the logic behind
9 this long time? I mean, it's easy to comment now.

10 Then the other question, again just
11 emphasizing what Dr. Liang was saying, was: Some of
12 these toxicities, particularly the renal when we have
13 it reduced to number parameters rather than the
14 numbers would be very interesting to see individual
15 patients, particularly the proteinuria, and what they
16 have.

17 ACTING CHAIRMAN HARRIS: Dr. Strand?

18 DR. JOHNSON: Let me -- I only have a
19 tautology which is sort of, you know, you balance
20 resources versus rigor. But we actually had a
21 discussion about this. Maybe that's what Vibeke is
22 going to respond to, about the 90-day call.

23 DR. STRAND: The 90-day call, yes. It was
24 because in 94-01 the patients complained rather
25 bitterly about coming every month to see the physician

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1 when they had mild to moderate stable lupus. So it
2 was agreed that, to conform with more regular
3 monitoring of lupus in this population, patients would
4 come on a quarterly basis, and outcomes would be
5 looked at from that point of view.

6 So the two baselines were mean, and then
7 it was a mean of the three follow-up visits.

8 To respond to one other point about
9 looking at the renal data, I think Michelle has
10 presented a lot of different ways of looking at it,
11 and I took your signals from the briefing document and
12 then took those patient numbers that had -- those
13 patients who had at least two signals, and I combined
14 the complements as one signal.

15 Then I went back to the database and
16 actually looked at creatinine clearances and looked
17 for any decrease from normal to abnormal or, if they
18 were abnormal, any decrease beyond that. And I looked
19 for total proteinuria from none to greater than 500
20 or, if they had some, then to greater than a gram, and
21 complement 3 levels, if they were normal at baseline,
22 to any decrease; and finally also hematuria, if there
23 was none to greater than 5, and if there was some to
24 an increase of 10.

25 So those are very, very stringent criteria

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1 to see whether there were patients who had multiple
2 ones of these parameters, and as you saw from the
3 slides that Michelle pointed out, there was a signal
4 in 94-01 that in part was probably accounted for by
5 baseline differences in pre-existing renal disease,
6 but there was no signal in 95-02.

7 DR. JOHNSON: Yes. I think the only fair
8 thing to say is there is nothing conclusory from my
9 analyses and nothing conclusory from yours. If you
10 really want to question the hypothesis of whether
11 there is a renal effect here, you do a trial that
12 addresses it head on.

13 DR. PETRI: Let me add to that, Earl,
14 though on several of the slides I showed you I give
15 you a lot of individual patient information on the
16 creatinine increase slide, but also the slide that
17 showed that patients went from normal but had a
18 doubling of protein at some point in the trial --
19 where were they at the last visit?

20 I actually gave you all the individual 24-
21 hour urine proteins on that slide.

22 DR. SILVERMAN: I appreciate it. It was
23 just more a general comment of the numbers themselves
24 sometimes can be useful. That was all.

25 DR. ANDERSON: I have a question just

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1 somewhat clarification but also suggesting a different
2 analysis. Should it wait until this afternoon?

3 ACTING CHAIRMAN HARRIS: Does it require
4 a reply?

5 DR. ANDERSON: No. No.

6 ACTING CHAIRMAN HARRIS: If it doesn't
7 require a reply, then let's leave it until this
8 afternoon. Can you remember it?

9 DR. ANDERSON: Oh, I think so, yes.

10 ACTING CHAIRMAN HARRIS: Go ahead. Go
11 ahead, why don't you?

12 DR. ANDERSON: Well, it's just that there
13 was an analysis that Dr. Johnson presented that the
14 sponsor didn't present, which was the SLEDAI greater
15 than 2 subset where there was adjustment made for
16 baseline prednisone, and the sponsor presented only an
17 unadjusted analysis.

18 I guess I was concerned about this,
19 because, okay, there was an imbalance at baseline in
20 prednisone when you restricted to the subset, but that
21 particular way of taking into account, given that the
22 outcome is so much -- you know, depends on a change in
23 prednisone is, I think, problematic. I think some
24 analyses that had stratified by both baseline
25 prednisone and by SLEDAI would have -- could have been

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1 more effective. I don't know whether those were done
2 or not.

3 DR. PETRI; It does require a response.
4 So if I may start the response, to address that issue
5 at the baseline imbalance, I showed you a slide where
6 we divided the patients by baseline prednisone, zero
7 to 15 and greater than 15 to 30, to show that you see
8 exactly the same pattern in the responses. But I
9 wanted one of our biostatisticians to address the
10 issue of whether you can put baseline prednisone into
11 a logistic regression model as a covariate to
12 appropriate adjust for the baseline imbalance.

13 DR. HURLEY: Yes. To answer that
14 question, we did look at that and looked at that
15 analysis, but what you find when you look at it is
16 that, within the groups, you have nonparallel
17 regression against the covariate. So actually what
18 happens is over 20 milligrams of prednisone the lines
19 converge, and so they are nonparallel.

20 So the basic assumption of covariate
21 adjustment doesn't work. So that's why we didn't.

22 DR. ANDERSON: But what about stratified
23 analysis, stratifying on both? I mean, you know,
24 making adjustment on both of those variables.

25 DR. HURLEY: But actually, the analysis

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1 that Dr. Petri showed you where she looked at the
2 SLEDAI >2 group --

3 DR. ANDERSON: So it wasn't on both at
4 once.

5 ACTING CHAIRMAN HARRIS: Basically, you're
6 asking about what happened to the other one.

7 DR. ANDERSON: Yes. Yes, of course.

8 DR. HURLEY: Certainly, what you'll find
9 is on the other one, since two-thirds of all of the
10 patients, the SLEDAIs <2 were responders, obviously,
11 you have a high response rate, no matter how you cut
12 that group.

13 DR. JOHNSON: So, Frank, are there other
14 criteria for the legitimate use of covariates in a
15 logistic regression analysis other than what was
16 specified in the protocol, i.e., that they pass some
17 sort of .05 imbalance at baseline?

18 DR. HURLEY: Well, you know, a fundamental
19 requirement for use of covariates is parallelism of
20 the regression within the different treatment groups.

21 DR. JOHNSON: And there's formal ways to
22 describe that?

23 DR. HURLEY: Yes.

24 DR. JOHNSON: Well, we should have put
25 them in the protocol then, sounds like.

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1 DR. HURLEY: Well, they are in every test
2 book. So --

3 DR. ELASHOFF: I want to make a related
4 comment, and that is neither the sponsors nor the
5 FDA's analyses make it clear which covariates went
6 into the model for each P value. So it's unclear if
7 the same covariates are used consistently from one
8 analysis to another.

9 We have been given no information on what
10 effect the inclusion of covariates has had on the P
11 values. Has it changed them a lot? Has it changed
12 them a little? As standard practice for both the
13 sponsor and the FDA, I think this information should
14 be made explicit. Thank you.

15 DR. JOHNSON: Some of that is in my
16 review, actually, but -- and as I recall, I think, in
17 the first trial there was incredibly trivial
18 differences between the use and the nonuse of the
19 covariates, and in the second trial the biggest area
20 where there was a difference was in this case that we
21 were just discussing.

22 ACTING CHAIRMAN HARRIS: Dr. Brandt.

23 DR. BRANDT: In looking at the composition
24 of the subject populations of the two studies, there
25 are roughly 20 percent African Americans, I think, in

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1 the first and maybe a little bit less than that in the
2 second, which reflects the composition of the United
3 States. But if we look at lupus, lupus is, what,
4 eight times more common in African American females
5 than in Caucasian females.

6 I wondered, were there any differences
7 that were apparent at all in looking at the data in
8 relation to race and, particularly, can you comment on
9 that with respect to the bone density studies?

10 DR. GURWITH: We did, obviously, look at
11 race. We don't have enough patients to really make a
12 difference. What we do see is there isn't a
13 difference in responder rates by race.

14 DR. BRANDT: Is that true also for the
15 bone density?

16 DR. GURWITH: We'll show you the slide.

17 DR. BRANDT: Was that true also for the
18 bone density studies?

19 DR. GURWITH: Bone density studies -- So
20 as you can see, the numbers, especially in the first
21 study, are quite small, 12 and 11 African Americans
22 per group. In the second study it's a little
23 different, a little more numbers, but the difference
24 between treatment groups still seems preserved. There
25 is a lower response rate in the placebo group in 95-

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1 02, but again these are small numbers.

2 Then, of course, we do have a study that
3 was referred to, and Michelle showed some of the data,
4 in Taiwan where essentially all the patients were
5 Chinese or Asian, and we saw good activity there. We
6 don't have enough Asian patients in the U.S. studies
7 to comment.

8 ACTING CHAIRMAN HARRIS: Dr. Silverman.

9 DR. SILVERMAN: In the 94-01 the median
10 dose in the GL and the 200 milligrams of the GL701 was
11 10. Did you do the analysis based on a 10 split of
12 the prednisone dose rather than a 15 split? As I
13 understand, your analysis was zero to 15 and greater
14 than 15. But the median, in fact, was 10. So did you
15 do an analysis of 10 and less, because it is easier to
16 achieve 7.5 from a median of 10 than it is to achieve
17 7.5 from a median of 15.

18 DR. GURWITH: So you are asking what the
19 patients look like just who received 10?

20 DR. SILVERMAN: No. I'm asking -- you did
21 your split to show that there is no difference between
22 zero and 15 and 15 to 30. Did you do a zero to 10
23 split and a greater than 10 split?

24 DR. GURWITH: Well, remember, the entry
25 criteria was 10 to 30. So there is nothing below 10.

1 DR. SILVERMAN: So 10 then. Half your
2 patients who received 200 milligrams of GL701 in your
3 first study received 10 -- if I understand what the
4 word median means. Therefore, did you split it at 10
5 and greater than 10, and is that possible to do?

6 DR. GURWITH; Of course, it's possible.
7 We haven't done it yet.

8 DR. LIN: I'm Stan Lin from FDA. I just
9 want to go back to the issue of covariate adjustment.
10 I think that the logistic regression was put into
11 place so that adjustment can be made, if necessary.
12 I think that, if you do have a baseline imbalance, the
13 adjustment needs to be taken into account.

14 I think also it points out the danger for
15 doing subset analysis. In this case, you know,
16 overall in the ITT there was no imbalance, and when
17 you go to the subsets either greater than 2, you do
18 see an imbalance. So that's the danger.

19 It also points to, when you go to 95-02,
20 even though there was a statement that if you look at
21 the SLEDAI <2 versus SLEDAI >2, the baseline, there
22 were no difference, but that's only the baseline you
23 don't see a difference.

24 That does not necessarily mean that the
25 outcomes will not be affected. Okay? So in that

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1 case, you do see a baseline difference. It's just
2 that you didn't see it, whereas in 94-01, if you go to
3 the subset, you saw it.

4 ACTING CHAIRMAN HARRIS: Thank you. Okay.
5 Now I know everybody is dying for lunch. It turns out
6 I have been assured that the public comment would be
7 no more than about ten or 15 minutes, and I'm
8 wondering if you can bear with us these few more
9 minutes for the public comment, and then we'll break
10 for lunch.

11 MS. REEDY: We have two electronic
12 submissions that I will read into the record. The
13 first is from Kathleen Arntsen, a lupus patient.

14 It says: "There is presently no drug used
15 to treat mild to moderate SLE exacerbations in those
16 patients who cannot tolerate or respond to standard
17 therapies such as aspirin, NSAIDS or in some cases,
18 plaquenil. Then it seems that approving Aslera for
19 this application would be supported by the FDA.

20 "Lupus patients have been subjected to
21 immunosuppressive, cytotoxic and corticosteroid
22 treatments for decades, which tend to be harsher than
23 the disease itself. In looking at these treatments
24 long term and their impending side effects of
25 malignancies, neutropenia, thrombocytopenia, liver

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1 toxicity, obesity, osteoporosis, diabetes, joint
2 replacements and atherosclerotic disease, one can see
3 that Aslera has fewer negative side effects. Facial
4 hair, acne, fat loss and hormonal changes seem mild in
5 comparison to the effects of the other drugs.

6 "Having just suffered from a 15-month
7 exacerbation of my SLE, I wish that I had the
8 opportunity to try Aslera. I did travel monthly to
9 Johns Hopkins Clinic for six months to participate in
10 another trial which did not help me.

11 "Many patients are limited in
12 participating in trials due to location, finances and
13 support of a travel companion. If this drug had been
14 previously approved, then my physician could have
15 tried it as a treatment for my flare, and I may not
16 have lost the past 15 months of my life.

17 "If Aslera can help even a small
18 percentage of lupus patients to improve clinically and
19 enable them to lower their use of corticosteroids,
20 then it should be approved. Since lupus patients have
21 so many sensitivities and idiosyncrasies, no drug will
22 work to alleviate symptoms in all patients. Improving
23 the quality of life for any patient should be a
24 desired goal here. It seems that Aslera can do that.

25 "Thank you. Kathleen Arntsen, lupus

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1 patient in Rochester, New York."

2 And this from Penny Wolf: "I would like
3 to comment on the pending approval of the Genelab drug
4 Aslera to be used in the treatment of mild to moderate
5 lupus.

6 "In reviewing the research and listening
7 to patient comments, I would have to say that there is
8 not much reason for great enthusiasm within the lupus
9 community for this particular drug. Its actual
10 benefit in terms of decreasing disease activity
11 appears to be minimal, and its prednisone sparing
12 benefits seem limited as well.

13 "The fact that Aslera's side effects are
14 few is a definite advantage, but without it offering
15 the elimination of other more toxic medications
16 (corticosteroids, methotrexate, etcetera), it is
17 difficult to work up a great deal of excitement about
18 the drug.

19 "It also appears one of the greatest
20 benefits of the drug is the unintended one of
21 increasing bone density. This is clearly an issue for
22 lupus patients, but there are, of course, other drugs
23 on the market specifically designed to treat
24 osteoporosis.

25 "Moreover, the side effects that have been

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1 documented with Aslera, such as facial hair growth and
2 acne, while not toxic, would hardly be appealing to
3 patients already dealing with such issues as
4 Cushingoid, weight gain, lupus lesions, etcetera.

5 "This might seem minor to the medical
6 community, but to the patients, such side effects can
7 be quite difficult to handle emotionally and would
8 doubtless discourage many from continuing or even
9 starting Aslera treatment.

10 "While none of these issues would prevent
11 Aslera from being approved, I do hope the patient
12 perspective will be taken into account in this
13 discussion. We support all efforts being made to
14 treat lupus. From our perspective, however, this drug
15 does not appear to offer much relief from what is
16 often a devastating, life altering disease. Thank
17 you. Sincerely, Penny Wolf, Lupus Foundation,
18 Piedmont Chapter."

19 ACTING CHAIRMAN HARRIS: One other
20 comment.

21 MS. REEDY: Actually, two. Ellen
22 Ignatius.

23 MS. IGNATIUS: Thank you. I am Ellen
24 Ignatius from the Lupus Foundation of America, and I
25 would like to read a brief statement and then another

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1 one which is in your packet.

2 Lupus is a chronic autoimmune disease that
3 can affect the body anywhere. Ninety percent of those
4 who have lupus are women, approximately 80 percent of
5 them diagnosed during childbearing years. It is a
6 disease that disproportionately affects women of
7 color, populations traditionally underserved in the
8 areas of health and essential human services.

9 There is no cure for lupus. There have
10 been no new treatments approved by the FDA
11 specifically for the treatment of lupus in 25 years.
12 Some of the treatments currently used for this disease
13 can be as devastating as the disease itself.

14 Steroids, while helping to treat the
15 inflammatory process of the disease, can have long
16 term side effects that can be damaging, and include
17 impaired wound healing, muscle weakness,
18 atherosclerosis, diabetes, vascular necrosis, and
19 osteoporosis.

20 A drug that can reduce or eliminate the
21 use of corticosteroids while improving disease
22 activity and symptoms holds great promise for those
23 who suffer with this devastating disease. The
24 risk/benefit ratio of GL701 with relatively few side
25 effects would be a great benefit to those who suffer

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1 with lupus.

2 The Lupus Foundation of America asks the
3 Advisory Committee to approve this drug and give those
4 who have lupus, especially those populations who are
5 underserved by health and essential human services, a
6 chance to reduce the devastation caused not only by
7 the disease but by the medications used in treatment.

8 I would like to read a formal statement
9 from Dr. Evelyn Hess:

10 "Dear Advisory Committee Member: I am the
11 Chair of the Medical Council of the Lupus Foundation
12 of America, Inc. and Vice Chair of the LFA's Executive
13 Committee.

14 "I have followed the progress of this drug
15 for the last few years and have heard many of the
16 reports on patient usage at meetings and in
17 publications. In my opinion, it would be an extremely
18 useful drug with relative few side effects which can
19 be of great benefit to SLE patients with mild to
20 moderate disease activity. I would hope that the
21 Advisory Committee will give it every consideration
22 and as a representative of the LFA, I hope that it
23 will be available for patients in the future.

24 "Thank you for your consideration.
25 Sincerely, Evelyn Hess, M.D., Professor of Medicine,

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1 Chair, Medical Council, Vice President, Executive
2 Committee, Lupus Foundation of America."

3 Thank you.

4 ACTING CHAIRMAN HARRIS: Thank you very
5 much.

6 That concludes our morning session. I
7 would like us to get back here in about an hour or
8 less -- an hour. Okay. I'm not at school. In one
9 hour. Thank you. That will be 1:40.

10 (Whereupon, the foregoing matter went off
11 the record at 12:47 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:43 p.m.)

ACTING CHAIRMAN HARRIS: Okay. Perhaps we can take our seats. I want to start this afternoon's session with a charge to the Committee that will be given by Dr. Jonca Bull.

DR. BULL: Good afternoon. The function of an Advisory Committee is to give FDA recommendations on the safety and efficacy data on the issues on an application that is brought to you for deliberation.

From the presentations this morning, I think you can appreciate that there are outstanding issues, some highlighted by our reviewers, I think, by Dr. Johnson on the weight of the evidence, the question raised by Dr. Lu as to whether or not additional studies are needed for the baseline SLEDAI>2 to support an efficacy claim, I think in our presentation from our biopharm reviewer as to whether or not there is any significance to the issue of the results from the ACTH stimulation test.

I think all of these are just a backdrop that we hope to get your input on, but focus more on the questions that have been -- that are in your packet that we will be addressing this afternoon.

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1 So without further ado on my part, I will
2 return the discussion to our Chair. Thank you.

3 ACTING CHAIRMAN HARRIS: Thank you very
4 much, Dr. Bull.

5 Obviously, I need not state the obvious,
6 that these have been very complex trials. I think the
7 nature of the analysis is going to be quite
8 challenging, and I invite, of course -- we'll invite
9 as much comment as we can as we move along here.

10 There are quite a few questions, and I
11 want to launch into the questions, and I'll start with
12 the first question, and I'll just read the first --
13 Well, maybe I'll read both together, and maybe we can
14 consider them together.

15 Please comment on the use of a SLEDAI>2 as
16 a criterion to define a clinically meaningful
17 population for study.

18 The second part of that question is: Can
19 a physician use such a disease activity index to
20 identify patients appropriate for therapy if a study
21 were to show a clinical benefit only for such a
22 subgroup of patients?

23 Actually, I am going to start by asking
24 our guest, one of our guests, to comment, who is Jack
25 Klippel. I am going to ask Dr. Klippel if -- In fact,

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1 I'll ask you to lead off.

2 DR. KLIPPEL: Well, aren't you nice. So
3 I'll begin this. So these are two separate questions,
4 and I think the answer to one of them is very easy,
5 and the answer to the other, to me, is much more
6 difficult.

7 That is, to use both -- To use some
8 setting of an activity measure as a criteria for a
9 clinical response, I think, is intuitively obvious.
10 You need some evidence of disease activity, whether
11 you are in an office taking care of an individual
12 patient or you are involved in a clinical trial.

13 I think all of us have had the frustrating
14 experience of being involved in trials where patients
15 begin with no disease activity whatsoever, and nothing
16 happens to them, and then you don't quite know where
17 you are.

18 So the answer about the use of a SLEDAI
19 criteria greater than 2 to define a clinically
20 meaningful population, I think that's a pretty easy
21 thing to establish.

22 What's much more difficult for me is can
23 a physician actually use this. I personally believe
24 that is going to be very difficult for a physician to
25 use in their office, for a couple of reasons.

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1 Lupus is at the moment treated
2 empirically, and there's a lot of judgment, and the
3 medical community is not accustomed at this point to
4 quantitating disease activity. So that, if that were
5 -- to try to then say that a drug is going to be
6 useful only in a certain setting and then to define it
7 very specifically like this, I think, is going to be
8 a great challenge.

9 My personal belief is that these kinds of
10 activity measurements have very little utility on an
11 individual patient basis for a physician in the
12 current climate.

13 ACTING CHAIRMAN HARRIS: Thank you very
14 much, Dr. Klippel. Good start. Can I pose a question
15 to you.

16 If that SLEDAI of 2 or less really is a
17 reflection of treatment with prednisone -- in other
18 words, these are people who have a SLEDAI of 2 or
19 less, but a number of them are treated with
20 prednisone. To achieve that sort of level, does that
21 matter in any way?

22 DR. KLIPPEL: Say that one more time.

23 ACTING CHAIRMAN HARRIS: Well, I think
24 that, certainly, in the first trial, from what I
25 understood, that patients may in fact be at a SLEDAI

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1 of 2 or less, but that is reflected because of the
2 prednisone that they are already getting. They may
3 have active disease, just that the disease is
4 suppressed at that level.

5 DR. KLIPPEL: Which is where I thought you
6 were going with the question, Nigel. To me, one of
7 the most interesting things that comes from this study
8 is that there are a lot of people who are maintained
9 on prednisone with little or no disease activity.

10 I think that will send a signal that in
11 that subgroup of patients there's not a lot of
12 justification for continuing prednisone, and one can
13 feel a little more comfortable removing the
14 prednisone. I think that's a sizable population.

15 So I think that, in and of itself, is
16 going to be very valuable to the therapy of lupus.

17 DR. WILLIAMS: I would agree. I think
18 that intuitively I would have said that there was not
19 a lot of active disease, and I think that the sponsors
20 have shown that in going back to look at those
21 patients.

22 The things that gave them the SLEDAI were
23 generally laboratory problems and not clinical
24 manifestations, and I don't think it is just because
25 they were suppressed by steroids.

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1 DR. SHERRER: I think, though, that that
2 group represents two distinct groups, although I think
3 the majority group are probably, just as you said,
4 people who have laboratory data and probably
5 fibromyalgia. But there is a group of patients who
6 had failed a steroid taper, presumably because of
7 manifestations of active disease, and those people are
8 different, I think, than the individuals who are on
9 prednisone simply because they have positive
10 serologies and they ache.

11 I think that, while for the purposes of
12 this study I think to separate them just simply by
13 greater than 2 or less than 2 on the SLEDAI is good,
14 I think if we want to look at that group more closely,
15 then we'll have to further subdivide them between
16 those who are maintained on prednisone because to
17 decrease prednisone leads to disease activity.

18 I think those are different patients than
19 the patients who are just simply on steroids to make
20 them feel good.

21 DR. WILLIAMS: I have a comment on that
22 second question. Dr. Klippel was saying that he
23 wasn't sure they could use it. I think that the
24 SLEDAI is not a difficult thing to fill out, and they
25 could use it.

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1 I don't think physicians will use it, but
2 you can use it in the study as a measure to show that
3 you have made a difference, and then say that the drug
4 is only indicated for someone who has active clinical
5 manifestations, and that can be determined.

6 DR. SILVERMAN: I have to agree with what
7 was said about people would not use it, but the
8 interesting thing I find about this -- If you look at
9 some of the clinical manifestations, you look at the
10 comment that over 60 percent of patients with placebo
11 were able to taper in the first study, you wonder.

12 This is going to sound like a funny thing
13 to say, but one of the added benefits of this drug
14 could be, in fact, in the patients who have a SLEDAI
15 of 2 would actually receive this drug and we can get
16 them off their steroids.

17 Now right or wrong, even if were a placebo
18 effect, we would actually do good. So it's an
19 interesting added benefit that it actually would do
20 patients a lot of good if the safety profile is good.
21 So, although scientifically it sounds not a clever
22 thing, but practically it's probably very practical.

23 DR. FIRESTEIN: I think physicians have in
24 the past shied away from filling out checklists in
25 order to decide if a patient was eligible or met

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1 criteria for using a particular drug. That's changed
2 somewhat in the last year or two, especially because
3 of third party payer issues.

4 So for instance, at least in California,
5 when we want to write one of the biologics, for
6 instance, for treatment rheumatoid arthritis, we
7 routinely have to fill out those sorts of forms, and
8 it turns out they are fairly easy to do.

9 I don't think that it's going to be a
10 major impediment. The SLEDAI, as you said, is very
11 easy to fill out a checklist and just go check a few
12 boxes, and it would be relatively simple to meet those
13 criteria.

14 ACTING CHAIRMAN HARRIS: Presuming the
15 drug company decided -- the managed care company
16 chooses to use the SLEDAI.

17 DR. FIRESTEIN: Well, if those are the
18 criteria that are in the labeling, then that would how
19 it would be used.

20 ACTING CHAIRMAN HARRIS: Okay, go ahead.

21 DR. WILLIAMS: If the drug is expensive,
22 the managed care people will use it as a means of
23 controlling it.

24 ACTING CHAIRMAN HARRIS: Dr. Liang. I'm
25 going to invite comment.

1 DR. LIANG: I have nothing to add, for a
2 change.

3 ACTING CHAIRMAN HARRIS: Okay. Dr.
4 Brandt.

5 DR. BRANDT: I think Jack is right about
6 the difficulty in getting physicians to use something
7 very simple. We had a go not very long ago of trying
8 to make Woolmach Pain, which is simply five questions
9 filled out by the patient, a vital sign on the chart
10 and have the patient fill that out and place it in the
11 hands of the physician along with the vital signs and
12 so on. It was totally ignored.

13 If it takes time -- Even if it doesn't
14 take much time, I think there's a mindset that has to
15 be overcome, and this is not a simple thing to do,
16 which is a sad commentary.

17 ACTING CHAIRMAN HARRIS: So if I've gotten
18 a sense of the discussion, I hear -- and tell me if
19 I'm wrong -- is that as far as SLEDAI>2 defining a
20 clinically meaningful population, there is a sense
21 here that, yes, that is indeed possible. The
22 utilization of a disease activity index, probably a
23 little less difficult to get doctors to do, but indeed
24 in the sort of clinical context in which we are
25 practicing medicine these days that a measure such as

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1 this may become more and more of a requirement.

2 So this may well become legitimate
3 clinical practice, you know, as we move along.

4 Is that -- Have I captured this? Are
5 there any other comments? Good, good.

6 Okay. We'll move to number 2. Let's
7 start with 2.a: Would it be important to show
8 efficacy at reduction of steroid dose before
9 considering a responder analysis such as that proposed
10 by the sponsor when assessing the steroid sparing
11 ability of a drug?

12 I'll read it again -- I guess you've read
13 it. Would it be important to show efficacy at
14 reduction of steroid dose, and so on. Perhaps I'll
15 ask one of our statisticians now to comment.

16 DR. ELASHOFF: I'm having trouble
17 understanding the question.

18 ACTING CHAIRMAN HARRIS: Yes.

19 DR. ELASHOFF: When you say prior to, do
20 you mean somebody should do a study of this before we
21 define such an outcome or do you mean that, if there
22 is a claim for a responder analysis, that it ought to
23 be supported by similar appearing results in terms of
24 reduction of dosage?

25 If you mean the second, definitely the two

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1 analyses ought to be consistent with each other, in my
2 mind.

3 DR. JOHNSON: I was trying to figure out
4 what the question meant, too. We went through many
5 morphs, I think. But I think it was along the lines
6 of the second proposal just a second ago here.

7 I think this was meant to probe about
8 whether one would inherently believe there should be
9 consistency between one endpoint and another, and
10 whether you would a priori believe that one endpoint
11 would be a more sensitive endpoint.

12 So if either one of them are going to
13 succeed, it would be the change in steroid dosage. I
14 think that was the thrust of the question.

15 DR. ANDERSON: So the two endpoints aren't
16 really identical in this case. The one is a percent
17 change, and it's sort of averaged over the whole
18 trial, I think. The other was -- No? Were they both
19 for last -- Last visit? Change to the last visit,
20 and the responder was -- I mean the last two or three
21 visits.

22 DR. ANDERSON: Well, it was a change from
23 the last visit from the first visit. I mean, it was
24 a change over the duration of the trial.

25 DR. ANDERSON: So I think they are

1 somewhat -- those two endpoints are somewhat
2 different. So it doesn't surprise me that they are
3 not totally consistent is what I'm thinking.

4 So if they were things that you could
5 really expect to be totally consistent, yes.

6 DR. PETRI: May I clarify for the
7 Committee? The endpoint for the 94-01 trial was
8 sustained prednisone reduction, which meant ≥ 2 months,
9 including the last visit.

10 There was a second primary endpoint, the
11 mean percent prednisone reduction at the last day. So
12 our presentation was that we thought the sustained
13 prednisone reduction was more important than the last
14 day, and we showed you an additional analysis of the
15 number of days during the whole trial that a lupus
16 patient was less than or equal to 7.5 milligrams to
17 support the sustained prednisone reduction endpoint.

18 DR. WILLIAMS: I think the two endpoints
19 ought to be consistent. However, I think this trial
20 was designed to better answer the first than the
21 second. With totally uncontrolled increases in
22 steroids, I don't know how you can determine what your
23 average steroid dose is.

24 So I think that, while I would expect them
25 to be consistent, I don't think the trial was designed

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1 very well to answer the second endpoint.

2 DR. SILVERMAN: I don't think they have to
3 be consistent. I think you can have a drug that
4 spares steroids that would be clinically very useful
5 which, unto itself, may have no direct benefit in
6 modifying the disease.

7 So I think that, whether they are
8 consistent -- if you get two trials that show the same
9 result, it's two uses of a drug, but a steroid sparing
10 agent per se which has no other -- but can significant
11 show steroid reduction is a very useful drug in a
12 disease such as lupus.

13 I was taught -- I'm not sure I believe it
14 anymore -- that azathioprine by itself had no role in
15 lupus, only as a steroid sparing agent.

16 DR. ELASHOFF: I think one could define
17 some sort of mean change to be more consistent in its
18 definition or the time period it covered, and then
19 that ought to be consistent with the percent
20 responder; or one could define something a little bit
21 more global like area under the dose response curve or
22 something like that. But I'm unhappy with a responder
23 -- with a percent responder if we can't define
24 something else in terms of the continuous measurement
25 that is reasonably consistent with it, even if this

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1 specific one might not be.

2 DR. TILLEY: If I could just make a
3 comment in general about this percent change: There's
4 a lot of looseness in the way people have been talking
5 about it. People have been talking about it as mean
6 change, and then it really is mean percent change.

7 There's statistical properties of a
8 percent change that are not reflected in mean change,
9 and that is, for example, the numerator and the
10 denominator are two normal random variables, and the
11 ratio of two normals is not normally distributed.

12 So we have already set up a funny
13 situation statistically. So I mean, I guess I'm less
14 uncomfortable with that percent change variable not
15 showing as much as they would like, given all the
16 things we've been talking about, plus the statistical
17 issues, than I am -- you know, the discord -- I'm less
18 uncomfortable with the discord.

19 I think they need -- if they have to do
20 work in the future, need to really go back and think
21 about, as Dr. Elashoff was saying, the way that they
22 talk about this prednisone sparing.

23 ACTING CHAIRMAN HARRIS: Any other
24 comment? Hopefully, that has been helpful.

25 Let's go to 2.b: Please comment on the

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1 differing trends seen for the two primary endpoints of
2 "responder" and "mean reduction in steroid dose" in
3 study 94-01.

4 Any takers and, of course --

5 DR. ANDERSON: This is related to what we
6 were saying before.

7 ACTING CHAIRMAN HARRIS: And 2.c: Please
8 comment on the trend seen for the subpopulation of
9 SLEDAI>2 for the "responder analysis" and the lack of
10 trend for the mean steroid dose analysis.

11 DR. WILLIAMS: These are all addressing
12 the same issue, and my answer would be the same. I
13 don't think this study was very well designed to look
14 at mean steroid dose, because you had an algorithm to
15 decrease it, but you could increase it by any amount
16 you wanted. So I think it was not designed very well
17 for that particular endpoint.

18 DR. FIRESTEIN: I was basically going to
19 say the samething. That is that you could have a few
20 outliers on the upside that could interfere with this
21 entire analysis, and that -- Maybe it would be better
22 to be looking at median reductions ex post facto in
23 order to try to make up for that one design problem.

24 DR. SILVERMAN: But it also addresses one
25 more point of are there patients who respond and don't

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1 respond to the drug, which could be lost in a mean
2 reduction; whereas, your number of responders would
3 pick that up.

4 So I think they are both -- They give you
5 different information, as I think of it. One would
6 tell me how many patients would meet a responder
7 criteria, whatever that definition is. Then globally,
8 does everybody get a response. But this could just
9 show you two dichotomous populations, the responders
10 and the non-responders.

11 So the fact that they don't meet doesn't
12 necessarily upset me. You would like to see it, but
13 it just means that there might be patients who do well
14 on the drug and some who don't.

15 DR. ELASHOFF: In this particular trial,
16 I am somewhat bothered by basing our conclusions only
17 on the SLEDAI>2 group, because that cut-point and the
18 decision to use that as a cut-point was based on the
19 data themselves, and even with a failure to break the
20 blind, I'm not sure but what they are introducing some
21 bias by doing that and proceeding on that.

22 I'm not convinced that that's acceptable
23 from a statistical point of view, or safe. Let's put
24 it that way.

25 DR. WILLIAMS: I agree statistically that

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1 they should have done this a priori. However, there
2 is a level where you can't expect -- If there is no
3 disease activity, you can't expect it to respond to
4 the drug. So that should have been determined before
5 the study started.

6 I agree that the level they picked -- I
7 would have guessed it would have been a little higher,
8 four, five or six. But that -- I understand your
9 comment there, but there is a level at which you can't
10 expect the drug to respond, because there is nothing
11 to respond to.

12 DR. TILLEY: I guess I'm less
13 uncomfortable, because they were very careful to talk
14 about it as an exploratory analysis with the second
15 trial being confirmatory of the information beyond
16 that cutoff point.

17 So I was less uncomfortable because of
18 thinking of it as an exploratory analysis.

19 DR. SILVERMAN: My only concern was --
20 Again, it's statistical, not clinical -- we didn't see
21 the data. How many of those patients who had between,
22 let's say, three and four would have been -- all
23 laboratory, thrombocytopenia, DNA, complement would
24 give you four as an example -- how many had clinical
25 features.

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1 I would be much more comfortable by
2 knowing there was this dichotomy we are assuming, but
3 it's only an assumption, that there is a laboratory --
4 that some of these two and threes had clinically --
5 these three and fours had clinically active disease.
6 In fact, they could be still clinically quiescent.

7 So I would like to see the clinical
8 correlation before I'm happy with the statistical
9 number of two, because if they would have gone in a
10 priori saying clinically we feel four is a clinical
11 number -- four and over, but it can only be lab. So
12 that's really a concern.

13 ACTING CHAIRMAN HARRIS: Okay. I wondered
14 if this is appropriate to ask. Suppose one were to
15 sort of try this again, I mean try a trial like this
16 again. Are there lessons perhaps one has learned here
17 in terms of design that one might -- and of course,
18 that is really being very hypothetical indeed, but
19 that there is a way one might go about this that might
20 avoid some of the concerns.

21 DR. ANDERSON: You could design the
22 endpoints more clearly so that -- I mean, this
23 continuous endpoint, I think -- I don't know what the
24 reasoning behind it was, but it seems, you know, in
25 hindsight to not been the best endpoint, best

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1 continuous type of endpoint that could have been
2 chosen.

3 Then I would say that, given the trial as
4 it was done, an analysis that included everybody but
5 did take into account imbalances, even if they weren't
6 completely, you know, sort of strongly significant
7 would have been a better analysis to do. But that's
8 not quite what you were asking. You were asking about
9 design.

10 DR. WILLIAMS: I think there's some
11 lessons to be learned from the rheumatoid arthritis
12 studies in that they could have determined at the
13 start of the study what they considered active
14 disease, and they could have also determined at the
15 beginning what they would have considered an adequate
16 response; because in rheumatoid arthritis studies we
17 consider what is going to be an adequate response.

18 We know there will be a certain placebo
19 response. So what are you going to accept as a
20 reasonable endpoint so that you can set your sample
21 sizes and so forth accordingly.

22 More importantly, as was mentioned earlier
23 today, we determine what is considered active disease.
24 While somebody mentioned the six joints, it can be
25 arbitrary, but at least there is a level that is set

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1 that you expect to see so many active joints if you
2 are going to call it active disease.

3 That's harder to do for lupus, but you
4 could do it based on the SLEDAI or the SLAM or
5 anything else, and I don't think 2 has to necessarily
6 be the number. But I think you ought to do that
7 before you start the study. I think amendments to a
8 protocol should be extremely rare.

9 DR. LIANG: Well, I don't know when this
10 study came out, but probably not too long ago. I
11 think it was last year. But Paul Fortan did that
12 exercise, in a sense, where he took scenarios of
13 patients and asked docs what would make you follow the
14 patient more closely, you know, change a dose,
15 consider new immunosuppression, and basically found a
16 cutoff around SLEDAI 2.

17 So you know, they guessed it, but they
18 guessed pretty close. I don't know if it was exactly
19 2. Maybe it was 3. What I'm saying is that I agree
20 with you that it would have been better to do it, but
21 then when it was done, it would have been to --

22 DR. JOHNSON: What was the SLAM cutoff,
23 Matt? Do you remember?

24 DR. LIANG: I think know. I think it was
25 about 5 to 7 maybe.

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1 DR. WILLIAMS: They don't have to be
2 right. They have to decide before what they are going
3 to do, because everybody uses 6 and 4, and we made
4 that up in CSSRD. We just said one day this is what
5 we are going to do, and everybody uses it. But it was
6 just -- I remember sitting in my office and doing it.

7 ACTING CHAIRMAN HARRIS: Well, I'm being
8 a bit bold here, because considering how much
9 discussion went into the design of this study
10 originally, I don't think we can solve anything in a
11 few minutes here.

12 DR. JOHNSON: Nigel, could I ask the
13 statisticians one more? I mean, is there agreement
14 amongst the three statisticians as to what would have
15 been the optimal definition of that second endpoint,
16 given -- No, there's not agreement?

17 DR. ELASHOFF: No. Well, we haven't
18 discussed it in any detail. If you want to use it to
19 reflect -- If you want to use it to support a
20 responder analysis --

21 DR. JOHNSON: No. It would be -- No.
22 What's the maximal steroid --

23 DR. ELASHOFF: But let me think, and then
24 we'll go. If you want to use it to support a
25 responder analysis, then it should be defined in a way

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1 consistent with the time period you use, and that sort
2 of thing. I don't think that we discussed in any
3 detail what you might do in terms of steroid sparing.

4 One thing, of course, is an area under the
5 curve kind of thing. There are a variety of things
6 you might do, and I think it would take some
7 discussion to decide whether we agreed with each other
8 or not.

9 DR. TILLEY: I think none of us feel
10 exactly comfortable with that percent change.

11 DR. ELASHOFF: No.

12 DR. TILLEY: I mean, of all the choices.

13 DR. ANDERSON: I could hazard a choice,
14 which -- You know, given that you have defined the
15 responder the way it was defined, then perhaps
16 something like the amount of reduction between
17 baseline and -- Well, the difference between the
18 baseline and the average over the last three months of
19 the trial in the amount of steroid, something like
20 that.

21 DR. JOHNSON: You mean the medians rather
22 than means.

23 DR. ANDERSON: Oh, probably. But
24 something along those lines would be closer to the
25 responder than just the change between the first day

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1 and the last day, and percent change at that.

2 DR. LIANG: But you would have difficult
3 with this dataset, because you don't have the
4 algorithm for escalation. Yours would be meaningless
5 without that other --

6 DR. JOHNSON: And I think the general
7 sense was -- as somebody had commented earlier -- that
8 an escalation algorithm would have shot the trial
9 right in the foot, that you wouldn't have accrued,
10 because physicians -- you wouldn't be able to get buy-
11 in on it.

12 Now you could always say, well, you've got
13 a control, but that invokes the fact that you hope you
14 have a big trial so things balance out.

15 DR. WILLIAMS: The data doesn't help you.

16 DR. LIANG: But I think that if you
17 actually discussed this rather than just summarize it,
18 it would be more helpful. In other words, describe
19 the mean reduction but also describe the situation of
20 the patients where it was increased, throw out the
21 crazy patient that Michelle pointed out. I mean, this
22 does not fall easy to statistical summary, I think.

23 DR. ELASHOFF: Well, apropos of that, you
24 could certainly make the histogram and present that
25 instead of just the mean or just the median.

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1 DR. SILVERMAN: I just back to one of
2 Ken's questions before or your question, actually,
3 Nigel. What can we learn from this? Well, one of the
4 things is exactly, as rheumatologists we should have
5 algorithms for increasing doses that we agree upon
6 and, if you don't meet the algorithm, your patient is
7 a dropout.

8 Well, in fact, that is a trial that is
9 being considered now in JRA where it's a steroid
10 sparing trial which has to allow those escalations.
11 There's a fixed dose escalation. If you are a patient
12 and your opinion can't meet that fixed escalation,
13 they are a failure.

14 So you can get, as -- I hope maybe we are
15 not as stubborn as lupologists, but you can get
16 rheumatologists in a room who are quite opinionated,
17 and agree to a dose escalation. It's not impossible,
18 and I would emphasize to my colleagues that this, to
19 me, emphasizes our need in the future -- not that we
20 should penalize this study in the least by the
21 comment, but we should to the future really emphasize
22 to our colleagues how critical this is.

23 I think the Committee should really
24 recommend strongly that this is so critical, because
25 here we are commenting on a crucial fact that the

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1 company's hands were tied, in fact.

2 DR. STRAND: I just wanted to clarify a
3 point, because when we were designing this in 1993, we
4 didn't know what would be a meaningful -- a clinically
5 meaningful outcome.

6 We certainly agreed that less or equal to
7 7.5 milligrams as sort of a stable decrease would be
8 physiologically meaningful and probably clinically
9 meaningful, but we also thought that perhaps something
10 like a 50 percent reduction, if you couldn't get
11 people down to 7.5, might also be clinically
12 meaningful.

13 That's where these two rather dichotomous
14 outcomes came from, and one was not really designed to
15 support the other. They were the only things that we
16 could do in the absence of data to try to understand
17 what could ultimately be considered steroid sparing.

18 The other point is that nobody knew what
19 active disease was. There had not been any trials
20 even with SLEDAI except the plaquinil withdrawal with
21 an early version of the SLEDAI that wasn't complete.

22 We talked about what might be mild
23 disease, what might be moderate disease, what might be
24 severe disease, but we didn't have a definition for
25 inactive lupus. We thought that if you withdrew the

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